PI: **Woolley, Josh**	Title: Mechanisms and Effects of Oxytocin on Social Cognition in Schizophrenia	
Received: 09/19/2011	FOA: CX11-020	Council: 01/2012
Competition ID:	FOA Title: CSR&D CAREER DEVELOPMENT AWARD (CDA-2)	
1 IK2 CX000758-01	Dual:	Accession Number: 3421280
IPF: 481016	Organization: VETERANS AFFAIRS MED CTR SAN FRANCISCO	
Former Number:	Department: Psychiatry	
IRG/SRG: MHBB	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 258,800 Year 2: 233,714 Year 3: 238,775 Year 4: 243,988 Year 5: 249,358	Animals: N Humans: Y Clinical Trial: N Current HS Code: 20 HESC:	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Joshua Woolley	San Francisco Veterans Affairs Medical Center	PD/PI
Daniel Mathalon	San Francisco Veterans Affairs Medical Center	Other (Specify)-Co-mentor
Wendy Mendes	University of California, San Francisco	Other (Specify)-Co-mentor
Sophia Vinogradov	San Francisco Veterans Affairs Medical Center	Other (Specify)-Primary Mentor
Sue Carter	University of Illinois at Chicago	Other (Specify)-O.S.C (Consultant)
David Leitman	University of Pennsylvania	Other (Specify)-O.S.C (Consultant)
Steven Porges	University of Illinois at Chicago	Other (Specify)-O.S.C (Consultant)
Kate Rankin	University of California, San Francisco	Other (Specify)-Co-mentor

OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE:
State Application Identifier:

1. * TYPE OF SUBMISSION
☐ Pre-application ☐ Application ☒ Changed/Corrected Application

2. DATE SUBMITTED:
Applicant Identifier:

4. a. Federal Identifier: GRANT10962554
b. Agency Routing Identifier: 662-San Francisco

5. APPLICANT INFORMATION
*** Organizational DUNS:** 078763885
* Legal Name: San Francisco Veterans Affairs Medical Center
Department: Research and Development
Division:
* Street1: 4150 Clement Street
Street2: Research-151
* City: San Francisco
County / Parish:
* State: CA: California
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 94121-1545

Person to be contacted on matters involving this application
Prefix: Mrs.
* First Name: Rebecca
Middle Name:
* Last Name: Yu
Suffix:
* Phone Number: 415-221-4810 x3687
Fax Number: 415-750-6906
Email: rebecca.yu@va.gov

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN):* 941160824

7. * TYPE OF APPLICANT: X: Other (specify)
Other (Specify): VA-ORD
Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
☒ New ☐ Resubmission
☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).
☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration
☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: ORD

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Mechanisms and Effects of Oxytocin on Social Cognition in Schizophrenia

12. PROPOSED PROJECT:
* Start Date: 04/01/2012
* Ending Date: 03/31/2017

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT:** CA-008

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION
Prefix:
* First Name: Joshua
Middle Name:
* Last Name: Woolley
Suffix:
Position/Title: Research Fellow
* Organization Name: San Francisco Veterans Affairs Medical Center
Department: Psychiatry
Division: Mental Health
* Street1: 4150 Clement Street
Street2: 116C-1
* City: San Francisco
County / Parish:
* State: CA: California
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 941211545
* Phone Number: 415-722-6662
Fax Number:
* Email: josh.woolley@ucsf.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	1,224,635.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	1,224,635.00
d. Estimated Program Income	0.00

16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious. or fraudulent statements or claims may subject me to criminal, civil, or administrative penalities. (U.S. Code, Title 18, Section 1001)

☒ *** I agree**

**** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.***

18. SFLLL or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: Mrs. * First Name: Lauren Middle Name:

* Last Name: Gee Suffix:

* Position/Title: Acting Administrative Officer

* Organization: San Francisco Veterans Affairs Medical Center

Department: Research and Development Division: Mental Health

* Street1: 4150 Clement Street

Street2: Research-151

* City: San Francisco County / Parish:

* State: CA: California Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 941211545

* Phone Number: 415-221-4810 x3687 Fax Number: 415-750-6906

* Email: Rebecca.Yu@va.gov

*** Signature of Authorized Representative**: Rebecca Yu

*** Date Signed**: 09/19/2011

20. Pre-application Add Attachment | Delete Attachment | View Attachment

424 R&R
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 08/31/2011

Project/Performance Site Location(s)

Project/Performance Site Primary Location ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: San Francisco Veterans Affairs Medical Center
DUNS Number: 0787638850000
* Street1: 4150 Clement Street
Street2:
* City: San Francisco
County: San Francisco
* State: CA: California
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 941211545
* Project/ Performance Site Congressional District: ca-008

Project/Performance Site Location 1 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Emotion Health and Psychophysiology Lab, UCSF
DUNS Number: 0948783370000
* Street1: 401 Parnassus Avenue
Street2:
* City: San Francisco
County: San Francisco
* State: CA: California
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 94143-0984
* Project/ Performance Site Congressional District: ca-008

Project/Performance Site Location 2 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Neuroimaging Center
DUNS Number: 0948783370000
* Street1: 1 Irving St.
Street2: Room A-C 109
* City: San Francisco
County: San Francisco
* State: CA: California
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 94143-0984
* Project/ Performance Site Congressional District: ca-008

VA Performance Sites

Additional Location(s) Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☒ Yes ☐ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☒ No

If yes, check appropriate exemption number. ☐1 ☐2 ☐3 ☐4 ☐5 ☐6

If no, is the IRB review Pending? ☒ Yes ☐ No

IRB Approval Date:

Human Subject Assurance Number: 00000280

2. * Are Vertebrate Animals Used? ☐ Yes ☒ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☐ Yes ☐ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. * Is proprietary/privileged information included in the application? ☐ Yes ☒ No

4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No

4.d. If yes, please explain:

5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

5.a. If yes, please explain:

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. * Project Summary/Abstract 1247-Project_summary.pdf Add Attachment Delete Attachment View Attachment

8. * Project Narrative 1248-Project_narrative.pdf Add Attachment Delete Attachment View Attachment

9. Bibliography & References Cited 1249-Bibliography_CDA.pdf Add Attachment Delete Attachment View Attachment

10. Facilities & Other Resources 1250-Facilities&Resources.pdf Add Attachment Delete Attachment View Attachment

11. Equipment 1251-Equipment.pdf Add Attachment Delete Attachment View Attachment

12. Other Attachments Add Attachments Delete Attachments View Attachments ☒

Schizophrenia is a devastating neurodevelopmental disorder that often emerges in young adulthood, interfering with normal social development. The diagnosis is present in 1-2% of the population and cuts across socioeconomic, demographic and national lines, affects veterans as well as civilians, shatters families, and costs society billions in lost income due to social disability. The social deficits associated with schizophrenia wreak havoc on the lives of individuals who develop the disorder, and these deficits independently predict worse clinical, functional, and occupational outcomes above and beyond positive symptoms and other cognitive deficits. Despite their clinical importance, social deficits are poorly understood and resistant to available treatment options. Furthermore, abnormal neural and autonomic responses to social stimuli appear to underlie these deficits in schizophrenia. For example, patients demonstrate decreased activity of the parasympathetic nervous system (PNS), increased activity of the amygdala, and decreased activity of the ventral prefrontal cortex (vPFC) when performing certain social tasks. The neuropeptide oxytocin plays an important role in social behavior in animals and humans, increasing pro-social behavior and improving social cognition in healthy and autistic individuals. Oxytocin has also been shown to have positive effects on neural and autonomic responses in healthy individuals. Despite its potential as a new treatment for social deficits and for remediation of neurophysiological abnormalities, few studies have examined the effects of oxytocin on social cognition and behavior or on neural and autonomic responses to social stimuli in patients with schizophrenia. We propose a series of experiments aimed at both investigating the underlying neurophysiological mechanisms of oxytocin's pro-social effects and quantifying the potentially clinically useful effects of oxytocin in patients with recent-onset schizophrenia. In order to accomplish these important goals, we will first examine the effects of a single dose of exogenous oxytocin on behavioral and psychophysiological responses using validated social cognition measures in 45 patients with recent-onset schizophrenia and 45 matched healthy comparison subjects. Next, we will examine if oxytocin administration normalizes neural responses to social stimuli by decreasing activity of the amygdala and increasing activity of the vPFC, using a well-studied fMRI social cognition paradigm in 36 new patients and 36 healthy comparison subjects. In both studies, we will also assess PNS activity as indexed by respiratory sinus arrhythmia (RSA) in order to test the hypothesis that oxytocin promotes social behavior by increasing PNS tone. If successful, these experiments will: 1) Provide novel and important data on the neurobiological factors that underlie social deficits in patients with schizophrenia; 2) Lead to larger clinical trials of oxytocin to improve clinical outcomes in young individuals with recent-onset schizophrenia; and 3) Provide a deeper understanding of the functional and mechanistic relationships linking interrelated neurophysiologic systems that support socially meaningful behavior in healthy and schizophrenic individuals. Studying young adult patients with recent-onset schizophrenia minimizes potential confounds of chronic illness including social isolation, drug abuse and neuroleptic use and maximizes the potential long-term impact of this intervention. Overall, this work has the potential to uncover mechanisms of social dysfunction in schizophrenia, and to identify a novel treatment for the difficult-to-treat social deficits of the illness.

Schizophrenia affects 1-2% of the world population, is one of the top ten causes of disability worldwide, and costs the US economy more than $63 billion yearly. The VA system treats approximately 100,000 veterans with schizophrenia each year, accounting for nearly 12% of the VA's total healthcare costs. Current treatments fail to address the social deficits of schizophrenia, which are stonger predictors of clinical outcomes than positive symptoms. A pharmacological treatment for the social deficits of schizophrenia would have considerable benefit for patients, their families, society, and the VA healthcare system. The pro-social neuropeptide oxytocin is a promising treatment for social deficits in schizophrenia. The current study will investigate the effects of oxytocin on social functioning in patients with recent-onset schizophrenia and is a critical step towards identifying whether oxytocin is a viable treatment option in schizophrenia, particularly for young veterans in the earliest phases of the illness, who have a high likelihood for functional recovery.

1. Brundtland GH. From the World Health Organization. Mental health: new understanding, new hope. *JAMA.* Nov 21 2001;286(19):2391.
2. Mancuso F, Horan WP, Kern RS, Green MF. Social cognition in psychosis: multidimensional structure, clinical correlates, and relationship with functional outcome. *Schizophrenia research.* Feb 2011;125(2-3):143-151.
3. Macdonald K, Macdonald TM. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harvard review of psychiatry.* 2010;18(1):1-21.
4. Goldman MB, Gomes AM, Carter CS, Lee R. Divergent effects of two different doses of intranasal oxytocin on facial affect discrimination in schizophrenic patients with and without polydipsia. *Psychopharmacology (Berl).* Jul 2011;216(1):101-110.
5. Averbeck BB, Bobin T, Evans S, Shergill SS. Emotion recognition and oxytocin in patients with schizophrenia. *Psychol Med.* Aug 11 2011:1-8.
6. Pedersen CA, Gibson CM, Rau SW, et al. Intranasal oxytocin reduces psychotic symptoms and improves Theory of Mind and social perception in schizophrenia. *Schizophrenia research.* Aug 11 2011.
7. Feifel D, Macdonald K, Nguyen A, et al. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. *Biol Psychiatry.* Oct 1 2010;68(7):678-680.
8. Schneider F, Gur RC, Gur RE, Shtasel DL. Emotional processing in schizophrenia: neurobehavioral probes in relation to psychopathology. *Schizophrenia research.* Sep 1995;17(1):67-75.
9. Loughland CM, Williams LM, Gordon E. Visual scanpaths to positive and negative facial emotions in an outpatient schizophrenia sample. *Schizophr Res.* May 1 2002;55(1-2):159-170.
10. Aleman A, Kahn RS. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? *Prog Neurobiol.* Dec 2005;77(5):283-298.
11. Harrington L, Siegert RJ, McClure J. Theory of mind in schizophrenia: a critical review. *Cogn Neuropsychiatry.* Aug 2005;10(4):249-286.
12. Sparks A, McDonald S, Lino B, O'Donnell M, Green MJ. Social cognition, empathy and functional outcome in schizophrenia. *Schizophrenia research.* Sep 2010;122(1-3):172-178.
13. Brune M, Abdel-Hamid M, Sonntag C, Lehmkamper C, Langdon R. Linking social cognition with social interaction: Non-verbal expressivity, social competence and "mentalising" in patients with schizophrenia spectrum disorders. *Behavioral and brain functions : BBF.* 2009;5:6.
14. Morgan D, Grant KA, Gage HD, et al. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. *Nat Neurosci.* Feb 2002;5(2):169-174.
15. Salokangas RK, Honkonen T, Stengard E, Koivisto AM. Subjective life satisfaction and living situations of persons in Finland with long-term schizophrenia. *Psychiatric services.* Mar 2006;57(3):373-381.
16. Carter CS. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology.* Nov 1998;23(8):779-818.
17. Feifel D, Reza T. Oxytocin modulates psychotomimetic-induced deficits in sensorimotor gating. *Psychopharmacology (Berl).* Jan 1999;141(1):93-98.
18. Caldwell HK, Stephens SL, Young WS, 3rd. Oxytocin as a natural antipsychotic: a study using oxytocin knockout mice. *Molecular psychiatry.* Feb 2009;14(2):190-196.
19. Keri S, Kiss I, Kelemen O. Sharing secrets: oxytocin and trust in schizophrenia. *Soc Neurosci.* 2009;4(4):287-293.
20. Rubin LH, Carter CS, Drogos L, et al. Sex-specific associations between peripheral oxytocin and emotion perception in schizophrenia. *Schizophrenia research.* Aug 2011;130(1-3):266-270.
21. Souza RP, Ismail P, Meltzer HY, Kennedy JL. Variants in the oxytocin gene and risk for schizophrenia. *Schizophrenia research.* Aug 2010;121(1-3):279-280.
22. Guastella AJ, Einfeld SL, Gray KM, et al. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry.* Apr 1 2010;67(7):692-694.
23. Andari E, Duhamel JR, Zalla T, Herbrecht E, Leboyer M, Sirigu A. Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *Proc Natl Acad Sci U S A.* Mar 2 2010;107(9):4389-4394.
24. Averbeck BB. Oxytocin and the salience of social cues. *Proc Natl Acad Sci U S A.* May 18 2010;107(20):9033-9034.
25. Luminet O, Grynberg D, Ruzette N, Mikolajczak M. Personality-dependent effects of oxytocin: Greater social benefits for high alexithymia scorers. *Biological psychology.* Jul 2011;87(3):401-406.

26. Tauber M, Mantoulan C, Copet P, et al. Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with Prader-Willi syndrome: a randomised placebo-controlled trial in 24 patients. *Orphanet J Rare Dis.* 2011;6(1):47.

27. Shahrokh DK, Zhang TY, Diorio J, Gratton A, Meaney MJ. Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. *Endocrinology.* May 2010;151(5):2276-2286.

28. Porges SW. The polyvagal perspective. *Biological psychology.* Feb 2007;74(2):116-143.

29. Beauchaine T. Vagal tone, development, and Gray's motivational theory: toward an integrated model of autonomic nervous system functioning in psychopathology. *Dev Psychopathol.* Spring 2001;13(2):183-214.

30. Smith TW, Cribbet MR, Nealey-Moore JB, et al. Matters of the variable heart: respiratory sinus arrhythmia response to marital interaction and associations with marital quality. *J Pers Soc Psychol.* Jan 2011;100(1):103-119.

31. Bal E, Harden E, Lamb D, Van Hecke AV, Denver JW, Porges SW. Emotion recognition in children with autism spectrum disorders: relations to eye gaze and autonomic state. *Journal of Autism and Developmental Disorders.* Mar 2010;40(3):358-370.

32. Beauchaine TP, Gatzke-Kopp L, Mead HK. Polyvagal Theory and developmental psychopathology: emotion dysregulation and conduct problems from preschool to adolescence. *Biological psychology.* Feb 2007;74(2):174-184.

33. Vaughan Van Hecke A, Lebow J, Bal E, et al. Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders. *Child Dev.* Jul-Aug 2009;80(4):1118-1133.

34. Houtveen JH, Rietveld S, de Geus EJ. Contribution of tonic vagal modulation of heart rate, central respiratory drive, respiratory depth, and respiratory frequency to respiratory sinus arrhythmia during mental stress and physical exercise. *Psychophysiology.* Jul 2002;39(4):427-436.

35. Egizio VB, Jennings JR, Christie IC, Sheu LK, Matthews KA, Gianaros PJ. Cardiac vagal activity during psychological stress varies with social functioning in older women. *Psychophysiology.* Nov 2008;45(6):1046-1054.

36. Chang JS, Yoo CS, Yi SH, et al. Differential pattern of heart rate variability in patients with schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry.* Aug 31 2009;33(6):991-995.

37. Fujibayashi M, Matsumoto T, Kishida I, et al. Autonomic nervous system activity and psychiatric severity in schizophrenia. *Psychiatry Clin Neurosci.* Aug 2009;63(4):538-545.

38. Berger S, Boettger MK, Tancer M, Guinjoan SM, Yeragani VK, Bar KJ. Reduced cardio-respiratory coupling indicates suppression of vagal activity in healthy relatives of patients with schizophrenia. *Progress in neuro-psychopharmacology & biological psychiatry.* Mar 17 2010;34(2):406-411.

39. Wrobel L, Schorscher-Petcu A, Dupre A, Yoshida M, Nishimori K, Tribollet E. Distribution and identity of neurons expressing the oxytocin receptor in the mouse spinal cord. *Neurosci Lett.* May 9 2011;495(1):49-54.

40. Grewen KM, Light KC. Plasma oxytocin is related to lower cardiovascular and sympathetic reactivity to stress. *Biological psychology.* Jul 2011;87(3):340-349.

41. Parker KJ, Buckmaster CL, Schatzberg AF, Lyons DM. Intranasal oxytocin administration attenuates the ACTH stress response in monkeys. *Psychoneuroendocrinology.* Oct 2005;30(9):924-929.

42. Feldman R, Gordon I, Schneiderman I, Weisman O, Zagoory-Sharon O. Natural variations in maternal and paternal care are associated with systematic changes in oxytocin following parent-infant contact. *Psychoneuroendocrinology.* Sep 2010;35(8):1133-1141.

43. Keri S, Kiss I. Oxytocin response in a trust game and habituation of arousal. *Physiology & behavior.* Feb 1 2011;102(2):221-224.

44. Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proc Natl Acad Sci U S A.* Dec 15 2009;106(50):21437-21441.

45. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry.* Dec 15 2003;54(12):1389-1398.

46. Norman GJ, Cacioppo JT, Morris JS, Malarkey WB, Berntson GG, Devries AC. Oxytocin increases autonomic cardiac control: moderation by loneliness. *Biological psychology.* Mar 2011;86(3):174-180.

47. Gamer M, Buchel C. Oxytocin specifically enhances valence-dependent parasympathetic responses. *Psychoneuroendocrinology.* Jun 3 2011.

48. Rauch AV, Reker M, Ohrmann P, et al. Increased amygdala activation during automatic processing of facial emotion in schizophrenia. *Psychiatry research.* Jun 30 2010;182(3):200-206.

49. Holt DJ, Kunkel L, Weiss AP, et al. Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophrenia research.* Feb 28 2006;82(2-3):153-162.

50. Holt DJ, Weiss AP, Rauch SL, et al. Sustained activation of the hippocampus in response to fearful faces in schizophrenia. *Biol Psychiatry.* May 1 2005;57(9):1011-1019.

51. Hall J, Whalley HC, McKirdy JW, et al. Overactivation of fear systems to neutral faces in schizophrenia. *Biol Psychiatry.* Jul 1 2008;64(1):70-73.

52. Taylor SF, Phan KL, Britton JC, Liberzon I. Neural response to emotional salience in schizophrenia. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* May 2005;30(5):984-995.

53. Williams LM, Das P, Liddell BJ, et al. Fronto-limbic and autonomic disjunctions to negative emotion distinguish schizophrenia subtypes. *Psychiatry research.* May 15 2007;155(1):29-44.

54. Lieberman MD, Eisenberger NI, Crockett MJ, Tom SM, Pfeifer JH, Way BM. Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. *Psychol Sci.* May 2007;18(5):421-428.

55. Ochsner KN, Ray RD, Cooper JC, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage.* Oct 2004;23(2):483-499.

56. Viviani D, Charlet A, van den Burg E, et al. Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. *Science.* Jul 1 2011;333(6038):104-107.

57. Vela C, Diaz-Cabiale Z, Parrado C, Narvaez M, Covenas R, Narvaez JA. Involvement of oxytocin in the nucleus tractus solitarii on central cardiovascular control: interactions with glutamate. *J Physiol Pharmacol.* Feb 2010;61(1):59-65.

58. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature reviews. Neuroscience.* 2011;12(9):524-538.

59. Pincus D, Kose S, Arana A, et al. Inverse effects of oxytocin on attributing mental activity to others in depressed and healthy subjects: a double-blind placebo controlled FMRI study. *Front Psychiatry.* 2010;1:134.

60. Gamer M, Zurowski B, Buchel C. Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proc Natl Acad Sci U S A.* May 18 2010;107(20):9400-9405.

61. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry.* Feb 2001;42(2):241-251.

62. Domes G, Heinrichs M, Michel A, Berger C, Herpertz SC. Oxytocin improves "mind-reading" in humans. *Biol Psychiatry.* Mar 15 2007;61(6):731-733.

63. McDonald S, Flanagan S, Rollins J, Kinch J. TASIT: A new clinical tool for assessing social perception after traumatic brain injury. *J Head Trauma Rehabil.* May-Jun 2003;18(3):219-238.

64. Kern RS, Green MF, Fiske AP, et al. Theory of mind deficits for processing counterfactual information in persons with chronic schizophrenia. *Psychol Med.* Apr 2009;39(4):645-654.

65. Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron.* May 22 2008;58(4):639-650.

66. Jennings JR, Kamarck T, Stewart C, Eddy M, Johnson P. Alternate cardiovascular baseline assessment techniques: vanilla or resting baseline. *Psychophysiology.* Nov 1992;29(6):742-750.

67. Guastella AJ, Mitchell PB, Dadds MR. Oxytocin increases gaze to the eye region of human faces. *Biol Psychiatry.* Jan 1 2008;63(1):3-5.

68. Gross J, Levenson R. Emotion elicitation using films. *Cognition & Emotion.* 1995;9(1):87-108.

69. Kring AM, Sloan DM. The Facial Expression Coding System (FACES): development, validation, and utility. *Psychol Assess.* Jun 2007;19(2):210-224.

70. Murphy D, Cutting J. Prosodic comprehension and expression in schizophrenia. *J Neurol Neurosurg Psychiatry.* Sep 1990;53(9):727-730.

71. Tottenham N, Borscheid, A., Ellertsen, K., Marcus, D.J., Nelson, C.A. Categorization of Facial Expressions in Children and Adults: Establishing a Larger Stimulus Set. Poster presented at the Cognitive Neuroscience Society annual meeting, San Francisco.

. April, 2002 2002.

72. Morris RW, Weickert CS, Loughland CM. Emotional face processing in schizophrenia. *Curr Opin Psychiatry.* Mar 2009;22(2):140-146.

73. Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine.* Jul 2000;44(1):162-167.

74. Talairach JaT, P. (1988) `Co-planar Stereotaxic Atlas of the Human Brain', Thiem. *Co-planar Stereotaxic Atlas of the Human Brain.* New York1988.

75. Brett M, Johnsrude IS, Owen AM. The problem of functional localization in the human brain. *Nature reviews. Neuroscience.* Mar 2002;3(3):243-249.

76. Lancaster JL, Woldorff MG, Parsons LM, et al. Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp.* Jul 2000;10(3):120-131.

77. Maldjian JA, Laurienti PJ, Burdette JH. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *Neuroimage.* Jan 2004;21(1):450-455.

78. Domes G, Lischke A, Berger C, et al. Effects of intranasal oxytocin on emotional face processing in women. *Psychoneuroendocrinology.* Jan 2010;35(1):83-93.

79. Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. *Schizophrenia research.* Dec 2010;124(1-3):13-21.

80. McGlashan TH, Johannessen JO. Early detection and intervention with schizophrenia: rationale. *Schizophr Bull.* 1996;22(2):201-222.

81. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci.* Jun 2002;5(6):514-516.

Facilities:

I will be conducting research at the San Francisco Veteran Affairs Medical Center (SFVAMC), the Emotion, Health and Psychophysiology laboratory (EHP) within the Psychiatry Department at the University of California San Francisco (UCSF) Parnassus Campus, and The Neuroimaging Center (NIC) at UCSF, which is a state of the art brain neuroimaging facility. The three sites are connected by a free shuttle service.

SFVAMC:

The SFVAMC has significant expertise and resources in schizophrenia research and is an ideal location to complete many of my proposed studies.

LABORATORY:

Dr. Vinogradov (mentor) has eight laboratory/research offices with adequate research and subject-testing space in Buildings 8 and 33 at the SFVA Medical Center. PCs of varying ages and capacities are networked throughout the laboratory with full T1 internet access. Rooms are equipped with desks, chairs, file cabinets, etc. Dr. Woolley's office is located in Room 9 of Building 33 at the SFVA Medical Center. Adequate office and laboratory space will be provided to the Dr. Woolley to complete the proposed studies.

COMPUTER:

Dr. Vinogradov has nine computers and three printers, which are networked to the system as office computers for database management and storage, statistical analyses, literature reviews, etc. Adequate computer resources will be provided to Dr. Woolley to complete the proposed studies.

OTHER:

Secretarial/Clerical support is available to Dr. Woolley at the SFVA Medical Center to help with his interface with the patient population. Computer technical support is available through on-site computer support from the Northern California Institute of Research and Education (NCIRE).

Emotion, Health and Psychophysiology Laboratory:

Dr. Mendes (co-mentor) directs the Emotion, Health and Psychophysiology Laboratory (EHP Lab) in the Psychiatry department at University of California San Francisco. This 1,200 square foot space in the Butler Building (immediately behind Langley Porter Psychiatric Insititute) comprises two experiment rooms (one especially suited for dyadic interactions), a central control room, and office space. Each participant room contains equipment to obtain non-invasive impedance cardiography (HIC-2000), continuous blood pressure measurement, electromyography, photoplethysmograph, skin temperature, electrogastrography, and skin conductance. The rooms are also equipped with state-of-the-art audio-visual equipment, which allows the researchers to surreptitiously observe and record participants during the experiment. During the experiments the researchers are in a centrally located control room in which the computers are housed to record incoming physiological data, monitors to observe participants, and computers to record participants' behavior. An additional room houses a -80 C freezer for the storage of saliva samples prior to sending them to be assayed. The system was built by Dr. Mendes at Harvard in 2004 at a total cost just over $300,000, and was recently updated in 2011 when Mendes moved from Harvard to UCSF. The lab also owns several ambulatory physiological recording devices, which we use for field and imaging studies. Dr. Woolley will have access to these facilities for the completion of the proposed studies (i.e. Aims 1 and 2).

Office:
Adequate office space for data analysis, team meetings and manuscript preparation is available for the PI at the Parnassus campus.

Computer:
The EHP laboratory currently houses 18 computers that have software that allows for scoring and editing physiological data, data entry, and analysis. The computers have several software programs required to edit, score, and ensemble physiological data. All software has been purchased or was written and developed by Dr. Mendes and will be available for the proposed research. One software program, Mindware, is a multi-module

physiological software system that allows for the off-line editing and ensembling of autonomic nervous system responses. The laboratory also has a license for the Linguistic Inquiry and Word Count (LIWC) program which is a text analysis software program that calculates the degree to which people use different categories of words across a wide array of texts and can determine the degree any text uses positive or negative emotions, self-references, causal words, and 70 other language dimensions. In addition, the lab has SAS and SPSS software that are used for data analysis. Adequate computer resources will be available to Dr. Woolley to complete the proposed studies.

CLINICAL:

Dr. Woolley has access to the Acute Psychiatric Services, the Psychiatric Rehabilitation and Recovery Center, and the Outpatient Clinics of the Psychiatry Service, of the SFVA Medical Center, and to the outpatient clinic of Langley Porter Psychiatric Institute (LPPI), at UCSF, and to Community Mental Health Clinics throughout San Francisco. At LPPI, the Prodromal Assessment, Research, and Treatment (PART) program is a uniquely strong resource for the evaluation, recruitment and study of young adults at risk for and suffering from psychotic illnesses. The PART clinic provides clinical assessment services, psychopharmacological consultation, medication management, individual & family therapy, referral services and case management for adolescents and young adults (12-30) with recent-onset psychosis or symptoms indicating ultra-high-risk for psychosis. The clinic is staffed by two adult psychiatrists and one child psychiatrist, a clinical psychologist, and a licensed Marriage and Family Therapist who functions as case manager and family therapist. PART conducts training and education seminars for community clinicians and is known as a resource on early psychosis throughout the SF Bay Area and is quickly becoming a nationally renowned center in the assessment and treatment of early psychosis. PART receives referrals from throughout Northern California and will be the major source of referrals for the proposed studies.

Scientific Environment:

UCSF is a world-class biomedical research and health science education centers. UCSF consistently ranks as one the top recipients nationwide and first among public institutions in National Institutes of Health (NIH) funding. The Department of Psychiatry at UCSF is a leader in psychobiological research and has consistently ranked among the top ten university departments in awards from NIMH and NIDA. Additionally, the psychiatry department at UCSF is rich with training opportunities for researchers with interest in neural, biological and genetic methodologies. The combination of the Langley Porter Psychiatric Institute (LPPI) at the University of California, San Francisco (UCSF) and the San Francisco Veteran's Affairs Medical Center (SFVAMC) offer a unique and powerful setting for me to both develop as a scientist and successfully complete the proposed studies.

The SFVAMC is one of the leading academic research institutions in the country. An affiliate of UCSF, it has the largest funded research program in the Veterans Health Administration, with more than $77 million in annual research expenditures. The Mental Health Service (MHS) research portfolio consists of approximately $20 million in active grants from NIH, VHA, DoD, and private foundations. MHS investigators, who are also In-Residence or Adjunct faculty in the Department of Psychiatry at UCSF, are engaged in high-impact clinical and translational research in PTSD, aging, substance abuse, and schizophrenia. The Interim Chief of the Service (Dr. Sophia Vinogradov) is an active NIMH-funded investigator with collaborations in the UCSF Department of Radiology. The MHS Associate Chief for Research (Dr. Krisine Yaffe) is also the Associate Chair for Research for the Department of Psychiatry, UCSF and holds the Royer Chair in Geriatric Psychiatry.

The MHS provides a range of clinical services to veterans, treating approximately 11,000 patients every year at its main San Francisco site and at 6 community-based outpatient clinics sited throughout northern California. The service is made up of approximately 120 FTE staff from a range of disciplines (including psychiatry, psychology, social work, nursing), many of who are also UCSF faculty members. Specialty clinical programs have been developed in geropsychiatry, PTSD, substance abuse, integrated care, women's mental health, mood disorders, and psychotic illness.

The MHS serves as a training site for medical students, residents, psychiatry fellows, psychology pre-doctoral and post-doctoral fellows, and trainees from other disciplines. It is consistently ranked as one of the best sites

for Psychiatry training by UCSF medical students, and the MHS Associate Chief for Education (Dr. Robert Daroff) is a member of the prestigious Academy of Medical Educators at UCSF.

Research Environment : UCSF is devoted solely to graduate education and research in the health sciences and is distinguished as one of the leading biomedical research and health science education centers in the world. In addition, UCSF is a major health care delivery center in northern California with a high volume of regional, national, and international patient referrals. UCSF is home to 11 research institutes, 1,500 laboratories, more than 3,000 ongoing research projects, and a library with a state-of-the-art computing and communications infrastructure. UCSF ranks in the top group of institutions of higher learning in total federal funding for research and training. In the past three decades, UCSF has evolved into a world-renowned biomedical research center with an annual budget of over $1.5 billion dollars to support its various research, teaching, and patient care activities. A large portion of the funds received is allocated for biomedical research. Research funding primarily is obtained on a competitive basis from the federal government. Additional research funding is received annually from the State of California, the University of California Office of the President, private research foundations, state and local government agencies, private philanthropy, and industry. The Department of Psychiatry at UCSF has an extensive research program. Current research funding for the department exceeds $35 million per year, with over 200 active research projects generated by 76 different PIs. The department has consistently ranked among the top ten university departments in awards from NIMH and NIDA.

The Department is particularly strong in supporting the career development of young investigators, as evidenced by the fact that, in recent years, the department has ranked highly in the number of Young Investigator Awards given by the National Alliance for Research in Depression and Schizophrenia as well as in the number of NIMH and NIDA Career Development Awards. The scientific efforts of the faculty are considerably enhanced by the general research ambiance of the campus as a whole and by the close proximity of the University of California, Berkeley and Stanford University. Specific activities in the Department of Psychiatry include molecular and cell biology, systems neuroscience, clinical psychopharmacology, as well as social, psychological, and epidemiological approaches to the study of mental illness. The Center for Neurobiology and Psychiatry, under the directorship of Dr. Samuel Barondes, an internationally recognized psychiatrist-scientist, provides a focus for interactions between clinical and basic scientists. Dr. Vinogradov's active collaborations with the Dynamic Imaging Laboratory (Dr. Gregory Simpson) and the Biomagnetic Imaging laboratory (Dr. Sri Nagarajan) will further provide the applicant with exposure and access to state-of-the-art resources in EEG, MEG, and fMRI data acquisition and analysis. Dr. Vinogradov's schizophrenia research laboratory and PART program will provide the applicant with all necessary administrative, methodological, and statistical support to carry out human subjects research with a clinical population.

Major Equipment

FMRI experiments will take place at the UCSF Neuroscience Imaging Center (NIC), a 20-minute shuttle ride from Dr. Woolley's laboratory. A Siemens 3 Tesla MAGNETOM Trio Tim MRI System is available in this new core research facility devoted to functional neuroimaging. The system is state-of-the art, with two 12-channel head coils, 16-channel parallel imaging, inline diffusion, perfusion, fMRI BOLD imaging, DTI and high-resolution anatomical imaging capabilities. The facility has hardware and software for presentation of visual and auditory stimuli, as well as the recording of button press, eye-movement, galvanic skin response, pulse oximetry, respirations and EKG. A staff physicist oversees all imaging research; a Siemens physicist is present at the site full time, and a staff research associate is available to assist with scanner operation. Dr. Adam Gazzaley serves as the director of the NIC and has established collaborations with Drs. Vinogradov and Mathalon. Image analyses are performed using MATLAB and spm2 software on PC systems that are housed in the lab of Dr. Mathalon, at the SFVAMC.

In this study, we will examine the behavioral effects and neurophysiological mechanisms of the pro-social neuropeptide oxytocin in patients with recent-onset schizophrenia. Such research is a necessary first step towards identifying whether intranasal oxytocin administration can serve as an adjunct treatment for social impairments in schizophrenia.

Schizophrenia emerges in adolescence, interferes with normal social development, and causes severely impaired social and interpersonal behavior. Moreover, the social deficits do not respond to available pharmacologic interventions. Abnormal neural and autonomic responses to social stimuli appear to underlie these deficits. For example, patients demonstrate hypo-activity of the parasympathetic nervous system (PNS), hyperactivity of the amygdala, and hypo-activity of the ventral prefrontal cortex (vPFC) when performing certain social tasks. The neuropeptide oxytocin, which plays an important role in promoting social behavior in animals, has been shown to improve social cognition, to increase PNS activity, and to decrease amygdalar activity, in healthy humans and in some patient populations. Despite its potential as a treatment for social deficits in schizophrenia and related disorders, few studies have examined the effects of oxytocin on social cognitive behavior or neural and autonomic responses to social stimuli in patients.

In order to accomplish this important goal, we will first examine the effects of a single dose of exogenous oxytocin on behavioral and psychophysiological responses using validated social cognition measures in 45 patients with recent-onset schizophrenia and 45 matched healthy comparison subjects. Next, we will examine if oxytocin administration normalizes neural responses to social stimuli by decreasing activity of the amygdala and increasing activity of the vPFC, using a well-studied fMRI social cognition paradigm in 36 new patients and 36 healthy comparison subjects. In both studies, we will measure PNS activity as indexed by respiratory sinus arrhythmia (RSA), in order to test the hypothesis that oxytocin promotes social behavior by increasing PNS tone.

Experiment 1: Measurement of Oxytocin Effects on Socially Relevant Behavior and Peripheral Physiology

Aim 1: To quantify the effects of exogenous oxytocin on social cognition and behavior in patients with recent-onset schizophrenia.

Hypothesis A: Patients and healthy comparison subjects will show enhanced social cognition (e.g., improved interpretation of paralinguistic and emotional cues, such as those involved in emotional or sarcastic communication) after administration of oxytocin versus placebo.

Hypothesis B: Patients and healthy comparison subjects will show increased attention to others' eyes and patients will exhibit increased facial and vocal affect expressivity after administration of oxytocin versus placebo.

Aim 2: To examine the effects of exogenous oxytocin on PNS activity in patients with recent-onset schizophrenia.

Hypothesis A: Patients and healthy comparison subjects will demonstrate increased PNS activity during social tasks after administration of oxytocin versus placebo.

Hypothesis B (exploratory): Patients and healthy comparison subjects' improvements in social cognition and behavior will be predicted by the degree to which oxytocin increases their PNS activity.

Experiment 2: Measurement of Oxytocin Effects on Neural Activation Patterns During Facial Emotion Processing

Aim 3: To examine the effects of exogenous oxytocin on patterns of neural activation as measured by fMRI during a well-characterized affect-labeling task in patients with recent-onset schizophrenia and healthy comparison subjects.

Hypothesis A: Patients will exhibit amygdalar hyperactivity and PNS hypo-activity when passively viewing faces, which will be normalized by administration of oxytocin.

Hypothesis B: Patients will exhibit hypo-activity of the vPFC when affectively labeling faces and this hypo-activity will be normalized by oxytocin administration.

Summary: These experiments will elucidate the neurophysiologic mechanisms of oxytocin's effects and determine the potential benefit of oxytocin as a novel adjunct therapy in recent-onset schizophrenia. By focusing on patients early in the course of illness, we will avoid potential confounds associated with chronic mental illness such as long-term social isolation, use of antipsychotic medications, and substance abuse. Additionally, early interventions have greater potential to improve the course of illness before patients' social networks have been eroded, leading to meaningful and sustained functional recovery.

A. Overview and Significance:

The purpose of this project is to investigate the behavioral and neurophysiological effects of the prosocial neuropeptide oxytocin in patients with recent-onset schizophrenia. Schizophrenia and other psychotic disorders affect approximately 3% of the world population[1] and the VA provides care to approximately 100,000 patients with schizophrenia each year, accounting for nearly 12% of the VA's total healthcare costs. The illness deprives patients of precious relationships, severely undermines lifelong academic and occupational function, and causes great stress for families and caregivers. While there has been progress in understanding the neurobiology of schizophrenia, current treatments are inadequate at reducing the morbidity of the illness. Given schizophrenia's severity, chronicity and progressive course, novel pharmacologic interventions are desperately needed.

Schizophrenia is associated with significant social cognitive and behavioral deficits such as impaired ability to produce and recognize facial and vocal emotions and difficulty interpreting other people's behavior and intentions. These deficits, sometimes referred to as "negative" symptoms, interfere with social relationships, impact community functioning, and are more common and more strongly associated with quality of life and functional outcomes than "positive" symptoms such as hallucinations and delusions, and "cold cognition" such as executive functioning and working memory[2]. Furthermore, patients with schizophrenia have abnormal autonomic and neural responses that underlie these social deficits and contribute to the morbidity and mortality of the illness. Current antipsychotic medications are ineffective at treating social deficits, improving social functioning or normalizing autonomic or neural responses in patients with schizophrenia. Oxytocin is a neuropeptide that is involved in attachment, parenting, and sociality in mammals; can be safely administered to humans; and has been shown to have pro-social and beneficial autonomic and neural effects in healthy and patient populations (see **Fig 1**). We propose a series of experiments aimed at both investigating the underlying neurophysiological mechanisms of oxytocin's prosocial effects and quantifying the potentially clinically useful effects of oxytocin in patients with recent-onset schizophrenia. If successful, these experiments will: 1) Provide high-impact data on the neurobiological factors that underlie social deficits in patients with schizophrenia, 2) Lead to larger clinical trials of oxytocin to improve clinical outcomes in young individuals with recent-onset schizophrenia, and 3) Provide a deeper understanding of the functional and mechanistic relationships linking interrelated neurophysiologic systems that support socially meaningful behavior in healthy and schizophrenic individuals.

B. Innovation:

There is growing interest in the effects of oxytocin administration as a treatment for social deficits in multiple patient populations including schizophrenia[3]. Recent work has shown that intranasal oxytocin improves aspects of social cognition[4-6] and reduces negative symptoms in patients with schizophrenia[7]. However, no study to date has investigated the ***interacting behavioral and neurophysiological*** effects of oxytocin, or examined the ***underlying mechanisms of oxytocin's prosocial effects*** in a patient population. Furthermore, the effects of oxytocin administration on neural responses to social stimuli have never before been studied in schizophrenia. The chief innovation in this project is the concurrent use of sophisticated social cognitive and social psychological techniques--including psychophysiology during social tasks and fMRI during facial emotion processing--to reveal the effects of oxytocin on socially relevant behavior, autonomic functioning, and brain activation in patients with schizophrenia. Second, the effects of oxytocin administration on eye-gaze patterns, autonomic physiology, behavior and neural activation patterns have never before been simultaneously investigated in any population.

C. Background:

C.1. Social Cognition and Behavior in Schizophrenia.

Social cognition refers to the processing of social information, including its encoding, storage, retrieval, and application, and is severely impaired in patients with schizophrenia. Patients are impaired at recognizing facial affect[8], likely due to abnormal eye-gaze patterns (i.e., patients gaze at information-rich eye and mouth regions less frequently than healthy subjects[9]), processing prosodic information[10] and understanding other peoples'

mental states[11]. Patients are also impaired at recognizing sarcasm and these deficits correlate with real-world social behavior[12]. Patients also have severe deficits in the expression of emotion including blunted facial affect and loss of prosody[10] (see **Fig 1**). These social deficits cause abnormal and ineffective social responses, rob the individual of precious relationships due to social rejection[13] and lead to isolation, which may mechanistically contribute to the positive symptoms of schizophrenia[14]. Conversely, living in social environments or having close friends is associated with enhanced quality of life and better outcomes in schizophrenia[15]. Despite their clinical importance, current treatments are ineffective at treating social cognitive and behavioral deficits in schizophrenia. A pharmacologic intervention that improves social functioning in patients with schizophrenia and helps them develop and maintain intimate social relationships would have significant benefits for patients, society and the VA health system.

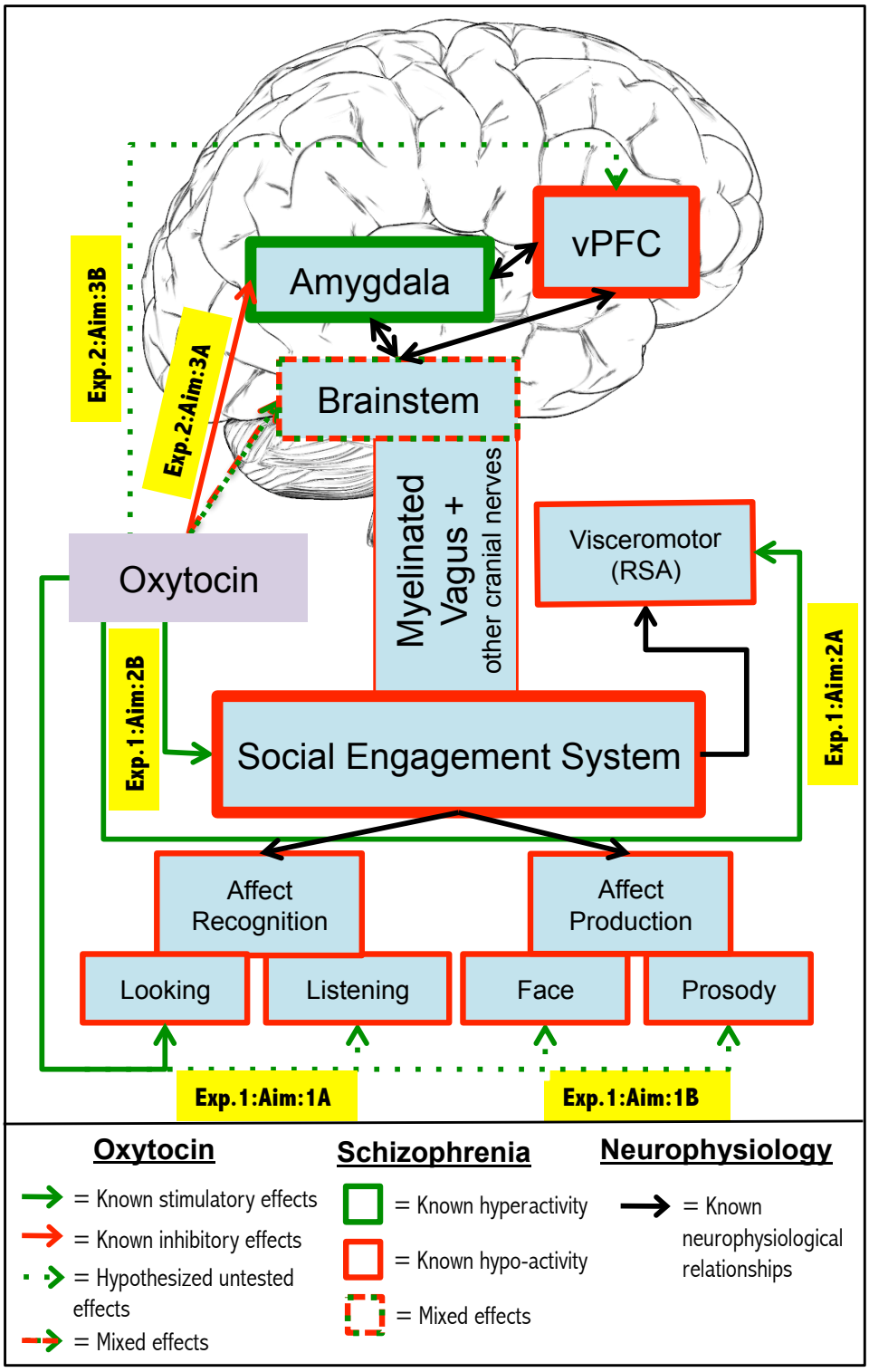


Figure 1. Model of interactions between oxytocin effects, schizophrenia, and key neural systems (see text in sections C.3 and C.4). Reciprocal amygdala-vPFC-brainstem connections regulate autonomic outflow from the brainstem. When the organism determines that the environment is safe (low amygdala activity), or uses frontal cognitive control mechanisms (high vPFC with low amygdala activity), brainstem circuits activate the PNS system, including the myelinated vagus and other efferent cranial nerves, which participate in the Social Engagement System. This activity promotes affect recognition and production through innervation of relevant sensory and motor systems. Respiratory Sinus Arrhythmia (RSA) reflects myelinated vagal innervation of the heart and is a latent measure of PNS activity. Oxytocin has known inhibitory effects on the amygdala, mixed effects on brainstem activity, and stimulatory effects on eye-gaze and affect recognition and increases RSA. Schizophrenia is associated with hyperactivity of the amygdala and hypo-activity of the vPFC, the Social Engagement System, and RSA. Note that known effects of oxytocin counteract multiple known deficits of schizophrenia (i.e., green arrows into red boxes and red arrows into green boxes). Also note, the primary pathway of oxytocin's effects remains unknown; however, oxytocin likely acts directly at multiple sites depicted on the diagram including the amygdala, brainstem and peripheral autonomic systems.

C.2. Oxytocin and Schizophrenia:

C.2.a: Dysregulation of the Endogenous Oxytocin System May Contribute to Social Deficits of Schizophrenia: Oxytocin is a nine amino acid peptide produced in the hypothalamus that has been implicated in bonding and sociality in mammals[16]. There is evidence from animal and human models that oxytocin may also play a specific role in the social deficits of schizophrenia. Psychotomimetic induced deficits in prepulse inhibition (PPI), an animal model for schizophrenia, are reversed by exogenous oxytocin[17] and oxytocin knockout mice develop social and PPI deficits that are also reversed by exogenous oxytocin[18]. In humans, peripheral oxytocin levels increase after a trust-related interaction in healthy subjects but not in patients with schizophrenia and this lack of response predicts negative symptom severity[19]. Furthermore, plasma oxytocin levels predict schizophrenic patients' ability to identify facial affect[20] and certain oxytocin receptor gene polymorphisms are risk alleles for developing schizophrenia and are associated with symptom severity[21]. These data support the hypothesis that oxytocin dysfunction may underlie some aspects of the social dysfunction seen in schizophrenia.

C.2.b: Oxytocin May Be An Effective Adjunct Treatment: Intranasal administration of oxytocin has powerful prosocial effects and is extremely well tolerated. After intranasal oxytocin administration, healthy subjects rate faces as more trustworthy, have better memory for faces, are better able to infer the mental states of others, have more positive communications, are more generous, gaze more at the information-rich eye region of faces, and demonstrate increased trust behavior when participating in a monetary trust game with human but not computerized opponents[3] (see **Fig 1**). Oxytocin administration to patients with autism improves facial and vocal affect recognition[22], normalizes social behavior in an online ball-tossing game[23] and increases gaze to the eye-region of faces[24]. Furthermore, oxytocin administration improves affect recognition in patients with alexithymia[25] and improves social behavior in patients with Prader-Willi Syndrome[26]. Finally, oxytocin signaling has direct effects on dopamine signaling[27], providing a potential mechanism for these positive oxytocin effects. These data indicate that exogenous oxytocin selectively improves various aspects of social cognition and behavior and raises the possibility that exogenous oxytocin may be an effective adjunct treatment for improving social deficits in patients with schizophrenia. Indeed, several small recent preclinical studies have found positive effects of oxytocin on social cognition in schizophrenia including improving affect recognition[4,5] and theory of mind[6]. Furthermore, a recent, small clinical trial found that three weeks of intranasal oxytocin decreased negative symptoms of schizophrenia[7]. While early work is promising, sample sizes are small and thus far there has been no integration of the observed behavioral effects of oxytocin with changes in neurophysiology in schizophrenia. ***We will test this hypothesis in Specific Aims 1A and B, Experiment 1.***

C.3. Oxytocin, Schizophrenia and The Polyvagal Theory:

C.3.a: The Polyvagal Theory Provides a Useful Model Linking Physiology with Social Cognition: The autonomic nervous system (ANS) is known to be relevant to social cognition and behavior, but has not been well studied in schizophrenia. Porges' Polyvagal Theory[28] proposes three functionally distinct, hierarchically ordered components to the ANS of mammals: the myelinated vagus, the sympathetic nervous system, and the unmyelinated vagus. Activation of the myelnated vagus is the major output of the parasympathetic nervous system (PNS) and this activity can be indexed through measurement of the variation in heart rate that occurs due to breathing, a phenomenon termed respiratory sinus arrhythmia (RSA). The myelinated vagus and special visceral efferents of other cranial nerves innervate muscles of the head and neck, respiratory centers, and the heart. Activity of this system--sometimes called the Social Engagement System--is typically calming and promotes social engagement by promoting facial affective expression, vocalization and listening (see **Fig 1**). When the organism determines that an environment is safe, the myelinated vagus is activated; PNS activity predominates over sympathetic responses; and the body prepares for homeostatic needs through deceleration of the heart, inhibition of fight/flight mechanisms, inhibition of the HPA axis, and reduced inflammation.

The Polyvagal Theory[28] posits that vagal activity and regulation are associated with superior emotion regulatory capacity, positive social emotions, and awareness of the social environment[29]. For example, high vagal tone (assessed by RSA at rest) is associated with more appropriate and intense emotional reactivity, better developmental outcomes and social skill development in newborns and preschoolers, higher marital

quality[30], and better affect recognition in patients with autism[31]. Conversely, low vagal tone is associated with negative emotionality, including hostility, anxiety, and aggression[32]. Greater ability to regulate RSA has been linked to greater social engagement in infants and fewer behavioral problems in patients with autism[33]. RSA levels increase during engaging social interactions, relaxation and positive mood induction in adults, but decrease during still-face paradigms in infants[34]. Finally, social isolation is associated with low RSA and acute social support reverses low RSA in depressed patients[35].

C.3.b: Schizophrenia Patients Have Low Respiratory Sinus Arrhythmia: While it is clear that vagal activity is important for social cognition and behavior in healthy subjects, and patients with schizophrenia have severe social deficits, no studies have investigated the relationship between RSA and social deficits in patients with schizophrenia. However, unmedicated patients with schizophrenia do have lower RSA at rest that is not corrected or altered after the initiation of first or second generation antipsychotic medications[36] but is negatively correlated with symptom severity[37]. Furthermore, unaffected family members of patients with schizophrenia have low RSA suggesting it is a core feature of the illness[38]. The Polyvagal Theory predicts that decreased PNS activity in patients with schizophrenia (as indexed by measures of RSA) will predict their social deficits, however, no research to date has explicitly linked the two in this patient population. ***We will test this hypothesis in Specific Aim 2A, Experiment 1.***

C.3.c: Oxytocin's Prosocial Effects May be Mediated Through Autonomic Physiology: The oxytocin system is well situated to coordinate and modulate autonomic functioning. The paraventricular nucleus of the hypothalamus (PVN), where oxytocin is produced, mediates autonomic homeostasis integrating afferent input into coordinated sympathetic and PNS responses. Projections from the PVN deliver oxytocin to the amygdala, hypothalamus, hippocampus, nucleus accumbens, raphe nuclei, locus coeruleus, vagal centers in the brain stem, sensory neurons, and the sympathetic chain in the spinal cord and oxytocin has been implicated in multiple autonomic functions including pain, micturition, uterine contractions, lactation, penile erection[39] and multiple aspects of cardiac functioning[40].

In mammals, including humans, affiliative social interactions elicit increases in oxytocin activity, which then activate and integrate 'anti-stress' responses including increased PNS activity. This promotes bonding, relaxation and growth, while reducing cardiovascular and neuroendocrine stress responsivity[40]. For example, postnatal oxytocin administration mimics the long-lasting cardiovascular changes caused by stroking in new-born rats and blocks the long-term negative effects of postnatal stress in rats[40] and social isolation in squirrel monkeys[41]. Furthermore, social isolation of the highly social prairie vole decreases RSA and increases depression-like behaviors and oxytocin administration blocks these effects[40]. In healthy humans, social stimuli such as massage and "warm touch" from a partner increase plasma oxytocin levels and higher oxytocin levels are associated with healthier cardiovascular responses to social stressors[40,42]. Furthermore, plasma oxytocin levels increase after a trust-related but not a non-social task and trust-related oxytocin increases are correlated with autonomic habituation suggesting that individual variation in oxytocin system functioning may determine more general autonomic regulation[43]. Additionally, oxytocin receptor gene polymorphisms are associated with decreased affect recognition and increased stress reactivity[44]. Finally, intranasal administration of oxytocin to healthy subjects inhibits social stress-induced increases in cortisol[45], increases RSA at rest[46] and increases PNS activity during affect recognition[47]. Taken together, activation of the oxytocin system appears to attenuate stress physiology and increase RSA, which indicates increased activity of the Social Engagement System. In fact, oxytocin-induced changes in brainstem regulation of autonomic output may be the mechanism for how oxytocin promotes social cognition and behavior. Given that patients with schizophrenia have low RSA and severe social deficits, oxytocin may be a particularly effective adjunct pharmacotherapy in this patient group. Our model for these proposed interactions is illustrated in **Figure 1**. ***We will test this hypothesis in Specific Aims 2A and B, Experiment 1.***

C.4. The Link Between Oxytocin, Autonomic Physiology, and Cortical Circuits:

While most previous work on social cognitive deficits in schizophrenia has focused on cortical functioning, subcortical and brainstem abnormalities likely interact with cortical mechanisms and contribute to the social impairments in schizophrenia. For example, in addition to the PNS dysfunction already discussed, amygdala-prefrontal circuits, which are critical for affect regulation, have reciprocal relationships with autonomic brainstem arousal circuits, and are disturbed in patients with schizophrenia[48]. While there is debate[10], patients

with schizophrenia appear to have abnormally increased[49] and sustained[50] amygdala activation when viewing fearful faces relative to low-level baselines, and when viewing neutral faces[51], as well as at rest[52] (see **Fig 1**). Furthermore, amygdalar dysfunction is associated with blunted affect and negative symptomatology[48] suggesting it is functionally linked to social deficits in schizophrenia. Finally, patients have hypo-activity of vPFC regions with concomitant autonomic hyperarousal during affect recognition tasks and this pattern is most apparent in patients with poor social functioning[53] (see **Fig 1**). In healthy subjects, labeling negative affect activates the vPFC and proportionally decreases amygdalar activity, likely reflecting a neural network whereby vPFC activity suppresses activation in the amygdala thereby helping to alleviate emotional distress[54,55]. Together, these data raise the possibility that heightened autonomic and amygdalar responses to emotional signals, without effective higher neural (e.g., vPFC) mechanisms for appraisal and cognitive control, could underlie social and emotional deficits in patients with schizophrenia.

Oxytocin administration may normalize amygdala-prefrontal-autonomic dysfunction in schizophrenia. In rats, oxytocin signaling modulates amygdalar projections to hypothalamic and brainstem nuclei that regulate the behavioral and physiological expression of fear[56] and oxytocin signaling within brainstem nuclei strongly regulates autonomic output[57] (see **Fig 1**). In healthy subjects, oxytocin administration decreases amygdalar activation in response to fear-inducing stimuli, reduces coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear stimuli[58], and increases vPFC activation during an affect recognition task[59] (see **Fig 1**). Furthermore, in one of the few studies to simultaneously measure eye-gaze during an affect recognition task, oxytocin administered to healthy subjects *decreased* activation of the anterior amygdala in response to fearful faces but *increased* posterior amygdala activation possibly due to increased gaze to the eye-region of faces[60] (see **Fig 1**). Additionally, oxytocin administered to individuals with generalized social anxiety disorder decreases their amygdalar hyperactivity in response to fearful or threatening faces[58]. Finally, oxytocin polymorphisms are associated with variation in amygdalar and brainstem volume in humans[58]. These data suggest that oxytocin administration will modulate brainstem activity leading to decreased amygdalar and increased vPFC activity in patients with schizophrenia while viewing emotional faces. ***We will test this prediction in Specific Aims 3A and B , Experiment 2.***

D. Preliminary Studies:

We have run preliminary experiments relevant to all three specific aims. Specifically, we have collected pilot data on the effects of intranasal oxytocin on social cognition and behavior, peripheral physiology, and eye-gaze patterns in adults with schizophrenia. Furthermore, our group has already used the affect-labeling task planned for Experiment 2 in an fMRI study of patients with treatment-resistant depression, and we have found that the task is inducing the expected brain activation patterns in depressed subjects and will be feasible to administer to young adults with schizophrenia.

D.1 Preliminary Data Relevant to Experiment 1 (Aims 1 and 2):

We administered oxytocin (40IU) and placebo to 22 adult patients with a chronic psychotic disorder (Age; Mean (SD): 43.1 (9.4), Education: 13.5 (1.7), 28.5% current smokers) and 8 healthy age-matched controls (Age: 42.6 (14.2), Education: 15.9 (2.1), 37.5% current smokers) in a randomized, double-blind, cross-over, within-subject design, with the two testing days separated by at least one week. We measured performance on the following tasks: Reading the Mind in the Eyes Test (RMET) and The Awareness of Social Inference Test (TASIT). Eye-gaze and ECG data were collected on a subset of these subjects. All subjects were in good general health, had no other neurological disorders, no substance dependence within last 6 months, were clinically stable, were on a stable dose of psychiatric medications for at least 4 weeks (patients only) and had a negative urine drug screen on each day of testing. Note that this patient population is older and has more chronic illness than the population that we are proposing to study in the current application. In order to assess the feasibility of Experiment 1, we have administered intranasal oxytocin to four young-adult patients with recent-onset schizophrenia and one age-matched healthy control in a paradigm similar to the proposed studies (data not shown).

D.1.a: General Issues: We have administered 40IU of intranasal oxytocin to over 37 individuals (26 with schizophrenia) over the last year. No subject has experienced any negative effects. Furthermore, our blinding procedure has been adequate and subjects cannot determine on which day they were administered oxytocin.

Both patients (52% guessed correctly) and healthy subjects (43% guessed correctly) were at chance level when asked to say which day they received oxytocin.

D.1.b: Methods

D.1.b.i: Social Cognition Measures:

A: The Reading the Mind in the Eyes Test (RMET) is a test of facial affect recognition where subjects select the mental states depicted in a series of 36 photographs of the eye region of faces[61]. Answers are selected from amongst four provided answer choices. This task has been used extensively in healthy and patient populations and intranasal oxytocin has been shown to increase performance on this task in healthy[62] and autistic individuals[22]. A paired *t*-test was used within each group to identify significant oxytocin-induced changes in performance.

B: The Awareness of Social Inference Test (TASIT) comprises short video clips of actors designed to assess the participants' ability to perceive social inferences, and allows for investigation of various components of social cognition[63] (for detailed description of methods see **E.1.e.i.A**). We analyzed oxytocin-induced changes in performance on the following social-cognitive components: *Think items* (TASIT SI-M and SI-E "think" probe questions, measuring representation of others' opinions/mental beliefs i.e., Theory of Mind); *Do items* (SI-M and SI-E "do" probe questions across all items, measuring representation of speaker's intention); *Say items* (SI-M and SI-E "Say" probe questions across all items, measuring what the speaker's intended message); *Feel items* (SI-E "feel" probe questions across all items, measuring emotion reading); *Sincere items* (SI-M sincere total score); *White Lie items* (SI-E white lie total score); and *Sarcasm items* (SI-M simple sarcasm and SI-E complex sarcasm scores). These subscales represent increasing levels of processing complexity and performance on the most complex subscales (*White Lies* and *Complex Sarcasm*) requires successful processing on the less complex subscales. Furthermore, the less complex processing levels do not require processing of emotion. A paired *t*-test was used within each group to identify significant oxytocin-induced changes in performance.

D.1.b.ii: Eye-Tracking: We quantified eye-gaze patterns of a subset of these adult subjects (10 patients and 4 controls) during completion of a facial memory task. Subjects saw 20 black and white images of faces for 5 seconds each and were instructed to memorize the faces for a subsequent memory task. We used the Eye-Link 2 head mounted eye-tracker.

D.1.b.iii: RSA: We measured electrocardiographic signals and calculated high frequency heart rate variability (RSA) in a subset of these patients (4 patients and 4 healthy controls) during completion of the social cognitive testing. Electrocardiogram data was collected during 5-minute blocks at baseline and 5, 10, 75 and 120 minutes after drug administration.

D.1.c: Results and Discussion:

		Schizophrenia Patients				Healthy Controls			
	Items	Oxytocin	Placebo	p value	Effect Size	Oxytocin	Placebo	p value	Effect Size
	RMET	68 (3)	65 (3)	0.10†	0.24	72 (5)	71 (4)	0.70	0.09
	TASIT								
Complexity ▼	Think (SI-M;SI-E)	76 (2)	71 (3)	0.05*	0.44	85 (4)	86 (2)	0.74	0.14
	Do (SI-M;SI-E)	74 (2)	68 (2)	0.003**	0.64	80 (4)	88 (3)	0.18	0.78
	Say (SI-M;SI-E)	73 (2)	68 (3)	0.12	0.44	77 (4)	86 (3)	0.04*	0.88
	Feel (SI-M;SI-E)	75 (2)	72 (2)	0.49	0.21	77 (5)	85 (3)	0.12	0.69
	Sincere (SI-M)	85 (3)	84 (4)	0.79	0.06	82 (7)	82 (5)	1.00	0
	White Lies (SI-E)	73 (4)	70 (3)	0.39	0.19	79 (4)	80 (4)	0.66	0.19
	Sarcasm (SI-M;SI-E)	70 (3)	64 (4)	0.05*	0.43	80 (3)	90 (3)	0.03*	1.01

Table 1. Oxytocin effects on social cognition (% correct (standard error)). † = $p<0.1$, * = $p<0.05$, ** = $p<0.01$

D.1.c.i. Social Cognition Measures:

A: RMET: As shown in **Table 1**, a single dose of intranasal oxytocin non-significantly improved patients' ability to recognize facial affect but had no effect on performance in healthy subjects. (The lack of oxytocin effects in healthy subjects may be due to a ceiling effect because oxytocin non-significantly increased performance on the hard items (68.1% vs 62.5%, p=0.31)). While still preliminary, these findings are consistent with previous work[22] and suggest that oxytocin administration can remediate facial affect recognition deficits in schizophrenia.

B: TASIT: Though highly preliminary, we found that a single dose of oxytocin significantly improves patients' ability to understand others' mental states (i.e. Theory of Mind, *Think-Verbal items*), intentions (*Do Items*), and to perceive sarcasm (*Sarcasm items*) **Table 1**). This is clinically promising because Theory of Mind abilities are correlated with functional outcome in schizophrenia[2] and patients' comprehension of sarcasm on the TASIT correlates with current social functioning[64] and lower personal distress and higher engagement and enjoyment in recreational activities[12]. Furthermore, this pattern of oxytocin-induced performance improvements suggests that exogenous oxytocin improves patients' social cognitive abilities "from the ground up", improving basic social cognitive processing (e.g. *Think* and *Do items*) as well as more complex processes (*Complex Sarcasm items*). Taken together, our findings provide initial support for using oxytocin as a pharmacological treatment for social cognitive deficits in schizophrenia. These promising data were collected on a small number of older adults with chronic schizophrenia who have been ill for decades; larger effect-sizes may be seen in response to oxytocin administration in the young-adult patients with recent-onset schizophrenia targeted in this proposal.

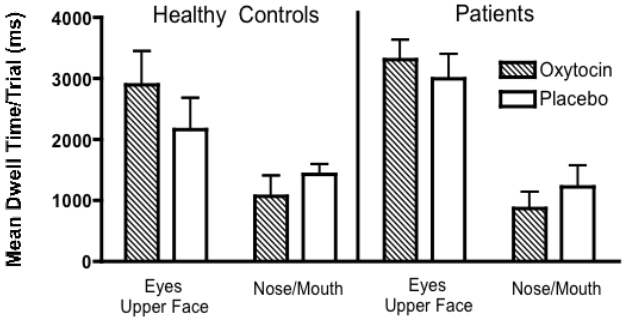


Figure 2. Effects of drug administration on gaze to the eye region of faces in patients and healthy controls.

We also found that intranasal oxytocin significantly *decreases* healthy controls' ability to recognize sarcasm and to interpret the intended meaning of speaker's speech (*Say items*). Notably however, oxytocin does not appear to have much effect on more simple aspects of social cognitive processing in healthy subjects (e.g. *Think* and *Do items*). This suggests that oxytocin may be specifically decreasing accuracy on complex, emotionally loaded, sarcasm items without altering cognitively simple (non-emotional) processes. Given oxytocin's known ability to increase trust in healthy subjects[65], our findings suggest that for healthy subjects, oxytocin administration may lead to taking speakers at "face value", leading to misinterpretation of sarcasm. Further work is necessary to investigate these interesting findings.

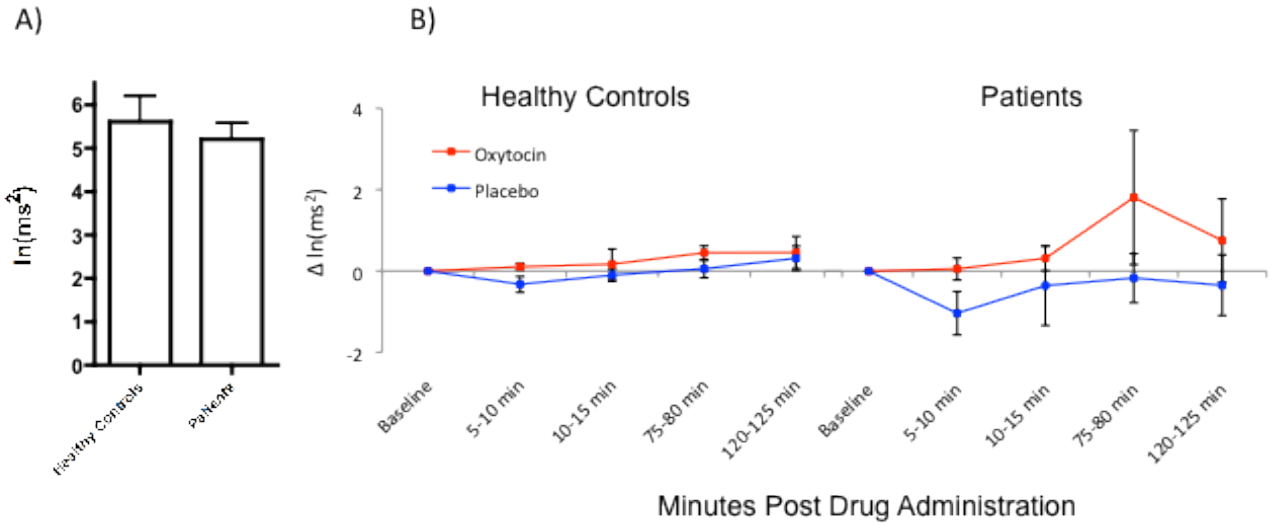


Figure 3. A) Baseline RSA. B) RSA changes from baseline in response to oxytocin and placebo administration. RSA expressed as the natural log of heart rate variability in the respiratory frequency band. Error bars represent standard error.

D.1.c.ii: Eye-Tracking: Figure 2 indicates that oxytocin may be increasing eye-gaze to the information rich eye-region of the face and decreasing gaze to the lower face in both patients and healthy controls. These early data support our hypothesis that oxytocin administration may normalize eye-gaze patterns in patients with schizophrenia.

D.1.c.iii: RSA: As shown in **Figure 3**, we found that patients with schizophrenia had non-significantly lower RSA at baseline compared to healthy controls and that oxytocin administration may increase RSA in the patients. This supports our hypothesis that patients have lower RSA and that oxytocin administration may normalize RSA in schizophrenia.

D.2. Preliminary Data Relevant to Experiment 2 (Aim 3):

With co-mentor Dan Mathalon, Ph.D., M.D., we have conducted pilot experiments using the Affect Labeling Task proposed to be used in Experiment 2. A modified version of Lieberman's Affect Labeling Task[54], consisting of three task conditions: Affect Labeling, Gender Labeling, and Passive Affect Observing, was given to 22 patients with treatment-resistant depression (Age: Mean ± SD = 39.8 ± 10.7; for detailed methods, see section ***E.2.g.i.***). We found that patients with treatment-resistant depression demonstrated bilateral amygdala activation during the Passive Affect Observe condition compared to the Rest Condition (**Fig 4A**) and right amygdala activation during Affect Labeling compared to the Rest Condition (**Fig 4B**). Furthermore, patients demonstrated greater vPFC (Broddmann's area 47) activity during Affect Labeling blocks compared to Gender Labeling blocks (**Fig 4C**). These results are consistent with those of Liberman et at.[54]. Specifically, viewing emotional faces is associated with amygdalar activity and labeling emotional stimuli (i.e., putting feelings into words) increases activity in the vPFC. As this patient population likely has dysregulation of these circuits, we did not expect to replicate all of Liebermann's effects in this treatment-resistant depressed sample. However, these pilot data demonstrate that our fMRI task is working as expected and demonstrates the feasibility of our proposed experiment using this task in conjunction with oxytocin administration in young adult patients with recent-onset schizophrenia.

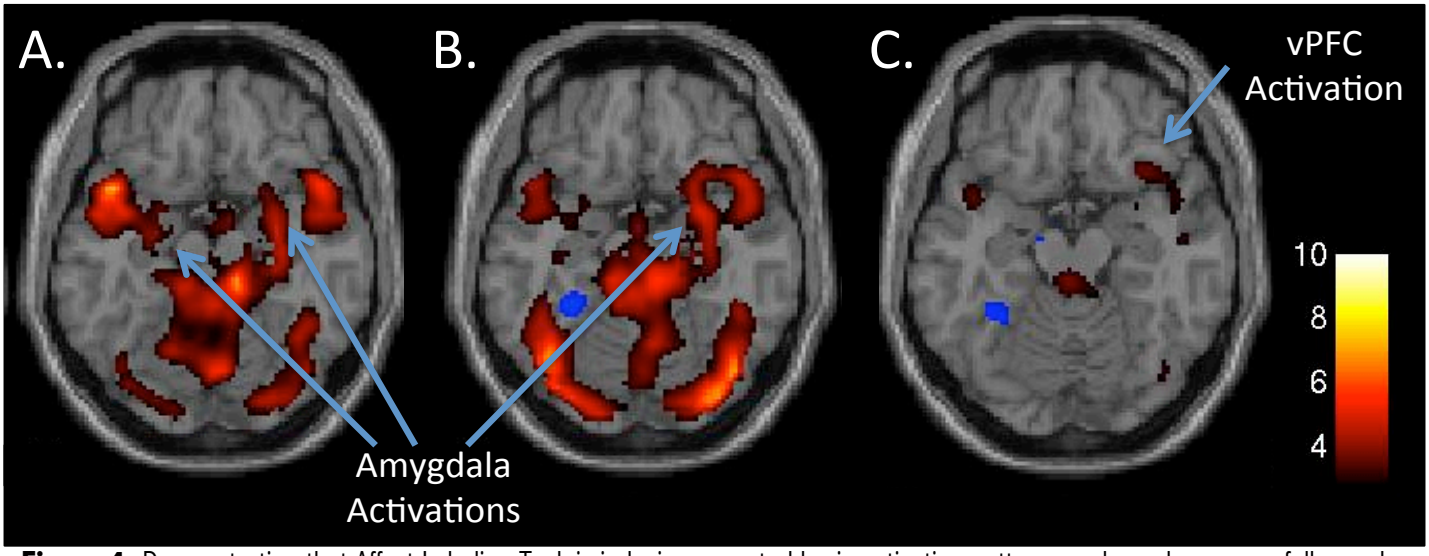


Figure 4. Demonstration that Affect Labeling Task is inducing expected brain activation patterns and may be successfully used in young individuals with recent-onset schizophrenia. Neural activation in patients with treatment-resistant depression during: A) Passive Affect Observation compared to the Rest Condition, B) Affect Labeling compared to rest and C), Affect Labeling compared to Gender Labeling. Images displayed at a voxel-wise threshold of 0.05, uncorrected.

E. Research Design and Methods

E.1. Methods and Procedures for Experiment 1: Measurement of Oxytocin Effects on Socially Relevant Behavior and Peripheral Physiology

E.1.a. Study Design Overview and Timeline: In order to quantify the effects of oxytocin on social cognition

and behavior (Aim 1) and PNS activity (Aim 2) in patients with recent-onset schizophrenia, we will administer oxytocin and placebo to patients and matched healthy comparison subjects and then quantify social cognition, eye-gaze, facial and vocal affect expressivity and PNS activity during two counter-balanced sessions (see **Figure 5**).

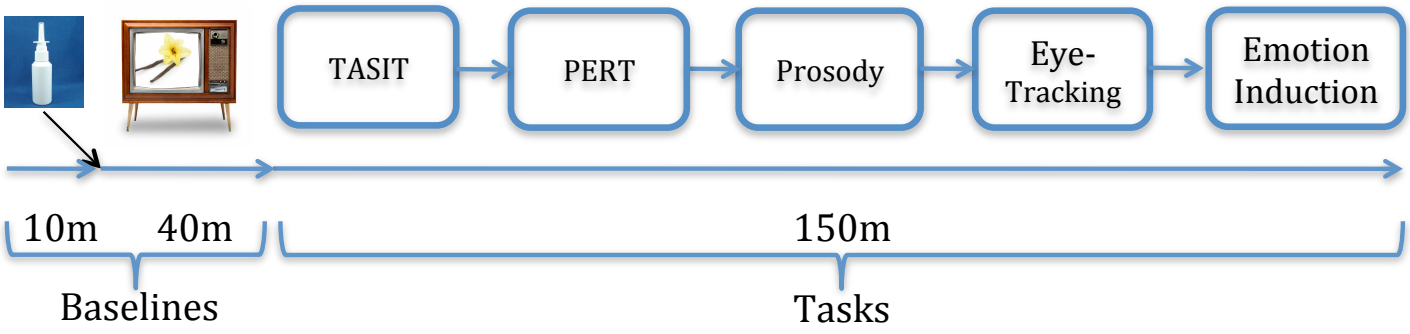


Figure 5. Overview and Timeline for Experiment 1.

E.1.b. Participants: We will recruit 45 male young adult patients with recent-onset schizophrenia or schizoaffective disorder and 45 healthy age-matched healthy comparison subjects.

E.1.c. Oxytocin/Placebo Administration: Intranasal oxytocin and placebo will be administered in a randomized, double-blind, counterbalanced order with a cross-over design, one week apart. Testing will follow drug administration after a waiting period of 40 minutes and continue for no longer than 2.5 hours. During the waiting period after drug administration and before testing, subjects will watch a neutrally affective video (The Appalachian Trail) because such "vanilla baselines" have been found to induce more similar behavioral and physiological states across participants than quiet baseline episodes[66].

E.1.d. Participant Compensation: Subjects will be compensated $10 per hour plus an additional $20 when they complete all study procedures. Given that testing should take no more than three hours on two separate days, each subject should make roughly $80 in total for participating in this study

E.1.e. Measures:

All tests will utilize different stimuli sets on the two days of testing, and stimuli set order will be randomized between subjects.

E.1.e.i: Social Cognition Tasks (Aim1A):

A. *The Awareness of Social Inference Test* (TASIT): We will use two TASIT subtests: Social Inference Minimal (SI-M) and Social Inference Enriched (SI-E). Both use short color video clips of professional actors[63] and are designed to assess the participants' ability to interpret literal and non-literal conversational remarks, as well as the ability to make judgments about the thoughts, intentions, and feelings of the speakers. SI-M comprises vignettes that represent everyday conversational exchanges that might typically occur between two people. The participant must attend to non-verbal paralinguistic information (e.g., intonation, facial expression, eye gaze, and gesture) in order to understand the otherwise ambiguous dialogue. In *sincere* exchanges (5 items), actors mean exactly what they say. In *simple sarcasm* exchanges (5 items), one of the actors means the opposite of what is said. The SI-E portion of the test is sixteen short videos with enriched contextual information provided to help the viewer comprehend the true state of affairs. In all of the clips, the message presented by the main speaker is contrary to what he/she believes. Half of the clips depict a *white lie*, where the main speaker attempts to hide information from another character. The other eight clips depict *complex sarcasm*, where the main speaker emphasizes the truth through both paralinguistic and contextual cues. For example, in a w*hite lie* exchange, the prologue to the main scene reveals an unfinished crossword puzzle (visual cue) that person A is working on, but this information is hidden from person B. Person A places the crossword puzzle upside down on the table, and when person B

turns around and asks whether person A has finished the crossword, person B responds with "oh yes, it was easy!" Subjects were expected to infer that because the crossword was not completed, person A intended to deceive. In a c*omplex sarcasm* exchange - in the prologue, the main speaker Ruth is observed conversing with her friend about how Gary has put on weight (verbal cue). Gary is unaware of this information. In the main scene, Gary asks Ruth whether he has put on weight, and Ruth responds while patting his large stomach, "no, you're as slim as ever!" in a sarcastic tone. The subject is expected to infer from the contextual information and paralinguistic cues that Ruth intended to make a sarcastic remark. At the end of each clip, the participant is required to answer four yes-no probe questions regarding the speaker's true belief ("think"), intention ("do"), what the speaker intended the listener to comprehend from their speech ("say"), and their emotional state ("feel").

B. In the Penn Emotion Recognition Test (PERT), subjects identify the emotion in 30 color photographs of faces displaying the six basic emotions and neutral.

C. In the Prosody Task, subjects listen to male and female actors vocally portraying happiness, sadness, anger, fear, and affection with weak and strong emotional intensity as well as no expression. Subjects must first identify the emotion portrayed and then rate the emotional intensity.

E.1.e.ii: Eye-Tracking (Aim1B): Subjects will be shown a series of 30 black and white photographs of faces and will be asked to look at the faces however they like while their gaze patterns are recorded. Oxytocin administration increases gaze to the eye-region of faces in healthy subjects during a similar task[67].

E.1.e.iii: Facial and Vocal Affect Expressivity (Aim 1B): During the Emotion Induction procedure, patients will view four, 2-3 minute long, emotionally evocative, color video clips[68]. These clips have been used in numerous studies and have each been shown to elicit sadness, fear, anger or amusement in healthy individuals. While watching these clips, subjects' facial expressions will be videotaped by a hidden camera and later coded using the Facial Expression Coding System (FACES)[69]. Coders will rate the valence, frequency, intensity, and duration of the subjects' facial expressions, defined as a change in the face from neutral to non-neutral and back to neutral. FACES coding yields six variables: frequency, intensity, and duration of positive and negative expressions. Two research assistants will code each tape, and adherence checks will be made periodically throughout the study to ensure high inter-rater reliability.

At the end of viewing each clip, subjects will describe the events and the emotional states of the people in that video clip for three minutes. These speeches will be audiotaped and then divided into six, 30-second clips. These clips will then be presented in a randomized order to two research assistants who are blind to condition and group. Using the methods of Murphy et al.[70], each 30-second clip will be coded for frequency, intensity, and duration of positive and negative prosodic expressions. Adherence checks will be made periodically throughout the study to ensure high inter-rater reliability. The entire 3-minute audiotape will be transcribed and analyzed using the Linguistic Inquiry and Word Count (LIWC) program, which is a text analysis software program that calculates the degree to which a text uses positive or negative emotion, self-referential, and causal words (http://www.liwc.net/).

E.1.e.iv: ANS Activity (Aim 2A and B): Continuous ANS responses will be measured using a variety of instrumentation including: electrocardiograph, respiratory band (which measures respiratory rate and depth), and continuous blood pressure monitoring (through an upper arm cuff). Primary signals collected will allow for the calculation of mean arterial pressure, systolic and diastolic blood pressures, heart rate, and RSA. Participants' RSA will be obtained during the 10-minute block immediately before drug administration, the 40 minute post-drug administration baseline, the Prosody Task, TASIT and the Emotion Induction Procedure.

E.1.f Data Analysis and Hypothesis Testing:

We will perform outlier analyses and regression diagnostics to assure adequate normality and homogeneity of variance in outcome measures. For all analyses, we will test for order effects and if significant, these will be included in the model.

E.1.f.i Power Analysis: Previous research suggests large effects of oxytocin on social cognitive functioning in multiple populations[19]. As our primary hypotheses relate to oxytocin effects in patients with schizophrenia, we performed our power calculations focused on within-group comparisons. Power calculations indicate that a sample of 45 subjects per group yields adequate power to detect the medium effect sizes that were found in our preliminary data (Cohen's d 0.43 for *Sarcasm items*) within groups (Critical t(44) = 2.01, α = 0.05, 1-β (power) = 0.80) and medium to large effects between groups (Critical t(88) = 1.98, α = 0.05, 1-β (power) = 0.80).

E.1.f.ii Aim 1A: ***Social Cognition:*** We will examine accuracy scores on tests of social cognition (comprehension of others' intentions (*Think* and *Do items*) and sensitivity to paralinguistic cues (*Sarcasm items*), as well as facial and verbal affect recognition: 1) within groups, after administration of oxytocin versus placebo, and 2) between schizophrenic patients and controls in a 2x2 repeated measures ANOVA (group x drug). We hypothesize that oxytocin administration will increase patients' social cognitive abilities including interpretation of others' thoughts and intentions and facial and vocal affect recognition. In healthy subjects, we hypothesize that oxytocin administration will increase affect recognition similarly to what has been shown previously (e.g. affect recognition) but will selectively decrease recognition of sarcasm. Within the schizophrenic group, the interaction between baseline patient characteristics, such as symptom severity, with responsiveness to oxytocin administration will be explored by modeling the impact of these mediators using proc GLM in SAS. We expect that oxytocin will improve social cognition more in patients with worse negative symptoms.

E.1.f.iii Aim 1B: *Social Behavior:*

Eye-Gaze: We will examine gaze patterns towards facial stimuli including eye-gaze duration, eye-gaze fixation count, and the number of saccades towards the eye-region, after administration of oxytocin versus placebo and between schizophrenic patients and controls in 2x2 repeated measure ANOVA (group x drug). We hypothesize that patients will gaze at the information-rich eye region of faces less than healthy controls and that oxytocin administration will increase gaze to the eye-region of faces in both healthy and patient populations. Furthermore, given that abnormal face-gaze patterns in patients with schizophrenia likely contribute to their social cognitive deficits, we will test our hypothesis that oxytocin-induced improvements in eye-gaze will predict oxytocin-induced improvements in social cognition in patients with schizophrenia using general linear modeling.

Facial and Vocal Affect Expressivity: We will examine facial expressivity during viewing of emotionally evocative videos in a 2x2x4 mixed-model (group x drug x clip emotion (sadness, fear, anger and amusement) using SAS proc Mixed. Given the known deficits in affective expressivity in schizophrenia, we hypothesize that patients will show decreased facial expressivity while watching the video clips compared to healthy controls. Furthermore, we hypothesize that patients will have less emotional prosody and use fewer emotional words in their descriptions of the video clips. Finally, given oxytocin's known neurophysiological effects and our hypothesis that oxytocin activates the Social Engagement System, we hypothesize that oxytocin administration will increase facial and vocal emotional expressivity in both groups for all emotions.

E.i.f.iv. Aim 2A: PNS Activity: We will examine PNS activity as indexed by RSA at multiple time points after administration of oxytocin versus placebo and between schizophrenic patients and controls in a mixed model including diagnostic group, time (6 time points, including pre-drug baseline), and drug (oxytocin versus placebo). We expect that patients will have lower RSA at baseline and throughout testing compared to healthy controls. Given oxytocin's known neurophysiological effects including decreasing amygdalar activity and stress physiology, we hypothesize that oxytocin administration will increase RSA in both groups but that the increase will be largest for patients with schizophrenia. Furthermore, we will investigate the relationship between RSA activity and social cognition using a mixed model including diagnostic group, time (6 time points, including pre-drug baseline), drug (oxytocin versus placebo) and accuracy on social cognitive tests. We hypothesize that subjects with lower RSA will perform worse on social cognitive tests.

E.1.f.v. Aim 2B: Relationship between oxytocin-induced changes in PNS activity and social cognition and behavior. RSA indexes PNS activity and PNS activity is the physiological substrate of the

Social Engagement System (see **Fig 1**). Therefore, we predict that oxytocin-induced increases in RSA will predict oxytocin-induced improvements in social cognition, eye-gaze, and facial and vocal affect expressivity. We will test this hypothesis using mixed modeling to determine if diagnostic group, time (6 time points), drug (oxytocin versus placebo), and RSA score can predict change in task scores (oxytocin minus placebo).

E.2. Methods and Procedures for Experiment 2: Measurement of Oxytocin Effects on Neural Activation Patterns During Facial Emotion Processing

E.2.a. Study Design Overview: Given that the neural responses to the social cognitive tasks used in Aim 1 are not well understood in patients with schizophrenia or healthy controls, we will use the Affect Labeling Task of Lieberman[54] to investigate the neurophysiological effects of oxytocin in patients with schizophrenia. This task has several advantages including that it has been well studied and elicits clear and reproducible effects on vPFC and amygdala activity in healthy subjects. Furthermore, we will include a neutral face viewing condition in order to explore the effects of oxytocin on schizophrenic patients' known amygdala hyperactivity to neutral stimuli[49]. In order to investigate the effects of exogenous oxytocin on neural responses to social stimuli, we will administer oxytocin and placebo to patients and matched healthy controls and quantify neural responses during this facial affect naming task using fMRI while we simultaneously measure RSA and eye-gaze.

E.2.b. Participants: We will recruit 36 young adult patients with recent-onset schizophrenia or schizoaffective disorder and 36 healthy matched comparison subjects. Healthy subjects will be included in order to test our hypothesis that patients with schizophrenia have hyperactivity of the amygdala and hypo-activity of the vPFC.

E.2.c. Oxytocin/Placebo administration: Intranasal oxytocin and placebo will be administered to the subject in a randomized, double-blind, counterbalanced order with a cross-over design, one week apart. fMRI scanning will commence 40 minutes after drug administration and continue for no longer than 2 hours.

E.2.d. fMRI Task Stimulus Presentation: We will use Presentation software for all task related stimulus presentations and behavioral response recording (http://www.neurobs.com/). Onset synchronization between the presentation of stimuli and the scan sequence is controlled by triggering the stimulus presentation computer with a pulse generated by the scanner at the beginning of the sequence. A pulse that indicates each repetition time (TR; one per brain volume) is continually monitored and recorded by the presentation and behavioral monitoring software packages to ensure millisecond synchronization between every stimulus and the scan acquisition over the course of the entire session. Visual stimuli will be presented using a projection system (5000 ANSI lumens) and displayed on a high-resolution screen located just behind the subject's head. Subjects view these stimuli using a mirror attached to the head coil. The mirror offers an unobstructed view embracing 60 degrees visual angle.

E.2.e. MRI acquisition: The following scans are acquired in the same sequence during each fMRI scan session using the Siemens Tim Trio with 12 channel head coil: 1) 3-Plane Localizer (256 x192 matrix, FOV=240 x 240; 5 slices each axis, 5 mm thick, # echos=1; scan time= 13 seconds), 2) 3-Dimensional T1-weighted Structural Scan (pulse sequence=MPRAGE; sagittal acquisition; FOV=220 x 220 mm; 256 x 192 matrix; 160 interleaved slices; 1.2 mm slice thickness; TR=2300 ms; TE=2.94 ms; Grappa Factor = 2; scan time=5:17), 3) T2 In-plane Scan (pulse sequence: TSE; scan plane=oblique axial, AC-PC aligned; FOV=220 x 220 mm; 256 x 256 matrix; 30 slices, interleaved; slice thickness= 4mm, skip 1mm; TR/TE: 6310ms/67ms; FA=149º; Turbo Factor=13; Phase encode: P/A; Grappa Factor =2; scan time=1:17), 4) FMRI Scans: (pulse sequence=ep2d_pace; scan plane=oblique axial, AC-PC, copy of the T2 in-plane prescription; FOV=220x220 mm; 64 x 64 matrix, single shot; 30 slices, sequential ascending order; slice thickness 4 mm, skip 1 mm; TR=2000 ms; TE=30 ms; FA = 77º; echo spacing= 0.50; phase encode: P/A; Coil combination method=sums of squares; spatial filtering=off).

E.2.f. Participant Compensation: Subjects will be compensated $10 per hour plus an additional $20 when they complete all study procedures. Given that testing should take no more than two hours on two separate days, each subject should earn approximately $60 in total for participating in this study.

E.2.g. Measures:

E.2.g.i. Affect Labeling Task: We will utilize a modified version of the experimental paradigm and block design of Lieberman et al.[54]. Subjects will undergo the paradigm twice, at least one week apart and different face images will be used on the two testing days. We will use only four of the six task conditions used by Lieberman: Affect Labeling, Gender Labeling, Passive Observing, and Shape Matching. We will also add a fifth condition of Passive Observing of neutral faces. The face stimuli will be selected from a standardized set of images[71]. Gendered names will be matched to the affect labels in multiple ways: there will be the same number of names and affect labels; both will be matched for word length; and for each affect label, there will be a name beginning with the same letter. During Affect Labeling and Gender Labeling, participants view target faces displaying emotionally evocative faces. During Affect Labeling, subjects choose the affect label from a pair of words shown below the picture that match the target face (e.g., angry or scared). During Gender Labeling, subjects choose the gender-appropriate name from a pair of names shown below the target (male or female names). Gender Labeling serves as a comparison condition to control for the cognitive processing demands of the Affect Labeling task. Half of the target faces will be male and half female. Passive Observing consists of viewing the emotionally evocative or neutral faces with no instruction except to watch each face as it is presented. Shape Matching consists of viewing a target shape and then selecting the matching shape from a pair of shapes located below the target. For each of the face processing task conditions except for Passive Viewing of neutral faces, 80% of the trials consist of a face depicting a negative emotional expression (fear or anger), and 20% of the trials consist of faces with positive expressions (happiness or surprise). This ratio of negative to positive faces has been used successfully in previous studies (e.g.,[54]). Negative faces more strongly induce amygdalar activity but the positive emotional faces need to be included to maintain an adequate difficulty level in order to engage vPFC circuits.

Participants complete three Affect Labeling blocks, three Gender Labeling blocks, three Passive Observing blocks, three Shape Matching blocks, and three Passive Observing of neutral faces blocks in pseudo-random order. Each block begins with a 3-s instruction cue indicating the task (affect labeling, gender labeling, shape matching, observing), followed by 10 trials of that task, randomly selected from a pool of trials, each 5s in length. Therefore, there will be a total of 30 trials of each task. Stimuli remain on the screen for the entire 5-second, and for task conditions requiring subjects to respond on each trial, they press one of two response buttons with the index and middle finger of their right hand. Blocks are separated by a fixation crosshair remaining on the screen for 10 seconds, plus a 10 second fixation at the beginning of each run and an 18 second fixation at the end of each run. The task is completed in three scanner runs. During each run, one of the blocks from each task condition is presented in a pseudo-random order, with a different block order for each run. Block orderings are counterbalanced across groups (patients and controls) and study day (session 1 and session 2) to avoid any order-effect confounds. Total task time is 13:00 minutes.

E.2.g.ii. Eye-Gaze and ANS Activity: Patients with schizophrenia find faces aversive (e.g., patients prefer to stand farther away from emotional faces than healthy controls), and avoid gazing at the eye region of faces[72]. Because no study to date has measured eye-gaze during an affect recognition task in the scanner in patients with schizophrenia, it is possible that the amygdala hypo-activation often found in patients during affective tasks is due to different amounts of eye-gaze during these tasks. Therefore, eye-gaze patterns will be measured throughout brain imaging. All data will be time-locked with the fMRI task and scan acquisition. Continuous ANS responses will also be measured using a variety of instrumentation within the scanner including: electrocardiograph and respiratory rate measurements. As RSA can be accurately calculated from as little as 30 seconds of ECG data (Stephen Porges, personal communication), RSA will be calculated for each 50-second task block. RSA will be calculated from ECG data collected during the pre- and post-drug administration waiting periods. Subjects' eye-gaze patterns will be quantified using a magnet compatible Long-Range Eye Tracking system from Applied Scientific Laboratories.

E.2.h. fMRI Processing Stream (Aim3A and B)*:* All image processing is performed using Statistical Parametric Mapping 5 (SPM5) (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College, London, UK) running in Matlab (The MathWorks, Natick, MA) on workstations located in Dr. Mathalon's image processing laboratory at the SFVAMC.

E.2.h.i. Preprocessing: The first five images of each time series are removed to compensate for saturation effects, and each time series is manually reoriented (i.e., affine transformations will be applied) to bring all images into approximately the same space as the SPM template image. Respiration and heart rate

data will be used to remove physiological noise from the fMRI BOLD time series using the RETROICOR algorithm[73]. Images are then slice-time corrected to adjust for timing differences of individual slices within each TR. Motion correction (realignment) is then performed on the slice-time corrected time-series. The mean functional image from the realignment step is co-registered to the high resolution T1 image, and this co-registration transformation is then applied to the entire functional time series. The T1 image is normalized to the Montreal Neurological Institute (MNI) T1 template using a 12-parameter affine transformation and 4x5x4 nonlinear basis functions, and the resulting parameters are used to anatomically normalize all of the individual functional images in the time series into MNI space. The images are subsequently resliced to 4x4x4 mm^3 using sinc interpolation and then spatially smoothed with a Gaussian filter, 5-8 mm FWHM. Smoothing facilitates inter-subject averaging by minimizing differences in functional and gyral anatomy, enhances the signal-to-noise ratio, and satisfies the assumptions of Gaussian random field theory implemented in SPM5.

E.2.i. Data Analysis:

E.2.i.i. Power Analysis: There are a number of fMRI task brain activation measures for which power could be calculated in the context of the current study. Since we lack specific effect size estimates for oxytocin effects on these measures, our approach to power was to consider a number of effect size scenarios in the context of an analysis of a specific region of interest (e.g., amygdala or vPFC) and task effect (e.g., Affect Labeling vs. Passive Observing) in a Group x Drug ANOVA model. First, we assumed that effect sizes for within-group changes from placebo to oxytocin would range between .1 to 1.2, with the patient group ranging between .6 to 1.2 and the healthy control group ranging from .1 to .5. Second, we examined the power to detect significant group differences assuming various combinations of within-group treatment effects. Based on this approach, we examined between-group effect size differences of .1 through 1.1. Third, power was calculated based on two-tailed significance tests with alpha set to .05, .01, or .001. Fourth, we report our power analysis for a sample size of 36 subjects per group, which we arrived at after considering the need to have reasonable power to detect effects of interest in the currently proposed study. The table below shows power estimates for various combinations of within-group change effect sizes in the patient and healthy control groups. We will have excellent to moderate power (96%, 87%, 64% for alphas of .05, .01, and .001, respectively) to detect a group difference effect size of 0.9, but moderate to low power (55%, 30%, 10% for alphas of .05, .01, and .001, respectively) to detect group difference effect sizes of .5. Our planned samples of 36 subjects per group will provide adequate power for the proposed fMRI study.

	Patient Placebo-Oxytocin Effect Size											
Healthy Control Placebo-Oxytocin Effect Size	**Effect Size**	**p<.05**				**p<.01**				**p<.001**			
		.6	**.8**	**1.0**	**1.2**	**.6**	**.8**	**1.0**	**1.2**	**.6**	**.8**	**1.0**	**1.2**
	.1	55%	83%	96%	99%	30%	62%	87%	97%	10%	33%	64%	88%
	.3	24%	55%	83%	96%	9%	30%	62%	87%	1%	10%	33%	64%
	.5	6%	24%	55%	83%	9%	9%	30%	62%	0%	1%	10%	33%

E.2.i.ii. General Considerations: In our experience conducting psychiatric patient fMRI studies, motion estimates for translation and rotation parameters are typically less than 2 mm and 2 degrees, respectively. Nevertheless, head motion, even at this small scale, may be problematic in functional imaging analyses. To address this issue, we will include the six realignment parameters (3 translation and 3 rotations) as covariates of no interest in the statistical model to remove variance due to movement from the general linear model.

E.2.i.iii. Task Activations (Aims3A and B): We will compare activations between the oxytocin and placebo conditions both within and between groups. First, given previous research, we predict that patients will demonstrate hyperactivity of the amygdala in response to social stimuli and hypo-activity of the vPFC during affect labeling compared to healthy controls. Furthermore, amygdala hyperactivity will be associated with decreased PNS activity and worse social cognitive deficits in patients with schizophrenia. Given oxytocin's demonstrated ability to decrease amygdala responses to fearful stimuli in healthy male subjects[58], we predict that oxytocin administration will decrease amygdala activity during passive face viewing in both healthy subjects and patients with schizophrenia. We are also interested in whether oxytocin will affect the inverse

relationship between amygdala activations and vPFC activations described by Lieberman et al.[54] during Affect Labeling tasks. We predict that oxytocin will decrease amygdala activation and increase vPFC activation in patients during affect labeling compared to passive viewing. Significant activations of the amygdala and vPFC will be correlated with PNS activity indexed by RSA. Furthermore, contrasts in activation patterns, PNS activity and activation pattern-PNS activity correlations will be examined between the oxytocin and placebo conditions both within and between groups. We predict that decreased amygdala activity will correlate with increased PNS activity.

E.2.i.iv. Model Estimation and Group Analyses: During model estimation, low frequency noise is removed with a temporal high pass filter (cut-off based on SPM defaults), and grand mean scaling is implemented to adjust the images for global differences in image intensity across subjects and scan sessions. We apply a fixed effects model to determine the location and extent of brain activations by comparing task and control conditions in each subject using multiple linear regression time series analysis. For block designs, as we are using in the current study, the reference waveform is a boxcar function convolved with SPMs canonical hemodynamic response function (HRF). These methods, combined with other analysis procedures implemented in SPM5, take advantage of the statistical power of the general linear model, and take into account corrections for temporal and spatial auto-correlations in fMRI data. Individual task condition beta images and contrast images reflecting differences in the beta estimates for key task-condition comparisons are generated for each subject as a result of these first level analyses. For group analyses, a random-effects model is implemented, which treats subjects as a random factor in order to make the findings generalizable to the population as a whole. Regression analyses of fMRI data against variables of interest (e.g., reaction time difference scores, symptom severity scores, baseline RSA etc...) will be performed in SPM5. While data analyses deriving group activation maps for key contrasts of interest will be performed within each subject group (patients and healthy controls) and under each drug condition (oxytocin and placebo), in order to describe the patterns of activation present in the data, the primary analysis to which all fMRI data will be subjected will be a Group (patients vs. controls) x Drug (oxytocin vs. placebo) repeated measures ANOVA. This will be implemented for each contrast of interest. Once this model is run, we will focus on sets of planned comparisons to address critical scientific questions: 1) Were there differences between the groups on the placebo days? We hypothesize that patients will show greater amygdala activation than healthy controls and decreased vPFC activation for all test conditions. 2) Was there a significant effect of Drug irrespective of Group? We expect oxytocin to decrease amygdala activity in both groups. 3) Was there a significant Group x Drug interaction? We expect oxytocin to have stronger effects in patients than healthy controls. For each contrast of interest, voxels that show a significant Group x Drug interaction based on a height threshold of $p<.05$ corrected for multiple comparisons using family-wise error rate or false discovery rate methods as implemented in SPM 5; alternatively we use an uncorrected height threshold of $p<.01$ or $p<.001$, followed by reliance on corrected cluster level significance testing (>50 voxels) will be saved into an explicit mask for further interrogation. Follow-up tests will then examine change between placebo and oxytocin conditions in each group within these masked brain regions in order to determine whether the patient group shows the predicted enhancements of emotional regulation and decreased amygdala hyperactivity when administered oxytocin. Depiction of the placebo to oxytocin changes in activation in each group for the interaction-masked brain activations effectively parses the Group x Drug interaction to provide interpretable results. To report activation regions, the Montreal Neurological Institute co-ordinate system used by SPM are first converted into Talairach and Tournoux space[74] with a Matlab program[75] and the converted coordinates are then fed into the Talairach Daemon Database[76] for anatomical labeling, verified by visual inspection. All coordinates will be reported in Talairach space.

E.2.i.v. Region of Interest Analyses: In addition to voxel-wise and cluster-level analysis of voxel-wise activation maps, *a priori* ROIs will be derived from WFU PickAtlas[77] and average voxel contrast values within these ROIs will be analyzed with ANOVA and regression analyses using standard statistical software packages such as SAS and SPSS. *A priori* ROIs will include amygdala and vPFC sub-regions including ventrolateral and ventromedial PFC.

E.2.i.vi. Autonomic Data Analysis: We predict that RSA will mediate the effects of oxytocin administration on neural responses. For each task, brain activation patterns will be analyzed with respect to drug administration, and task-block RSA for each block type (e.g. Affect Labeling) will be entered into the model as a parametric modulator. Beta-weight maps will be calculated allowing us to determine RSA-neural

activation relationships for each task type. Furthermore, the task specific beta weights will be pooled in order to determine RSA-neural activation pattern relationships irrespective of task type. Given that RSA is a latent measure of the Social Engagement System and oxytocin administration is hypothesized to increase activity of this system, we predict that higher task-block RSA will be associated with lower amygdalar and higher vPFC activity during emotional task blocks (Passive Viewing and Affect Labeling).

E.2.i.vii. Eye-Gaze Analysis: We will also examine eye-gaze patterns towards facial stimuli including eye-gaze duration, eye-gaze fixation count, and the number of saccades towards the eye-region, after administration of oxytocin versus placebo and between schizophrenic patients and controls in 2x2 Repeated Measures ANOVA (group x drug). Given that patients with schizophrenia have altered face gaze patterns[13] and oxytocin administration appears to increase gaze to the eye-region, which alters amygdala activation patterns[60], it is important to control for the location and duration of eye-gaze during the fMRI tasks. Therefore, we will subdivide task blocks into times when the subject is looking at the eye region versus times when they are not. This will be done by creating epochs of eye-gaze. Then, we will subject the fMRI data to a Group (patients vs. controls) x Drug (oxytocin vs. placebo) repeated measures ANOVA for each task only using data from eye-gaze epochs. This will quantify neural patterns of activation during eye-gaze epochs. These analyses will begin to elucidate the relationship between disease state, task demands, oxytocin and facial gaze patterns.

F. Subject Selection and Recruitment:

F.1.a. Participants: We will recruit 81 (45 for Experiment 1 (Aims 1 and 2) and 36 for Experiment 2 (Aim 3)) male young adult patients with a recent-onset psychotic disorder and 81 (45 for Experiment 1 (Aims 1 and 2) and 36 for Experiment 2 (Aim 3)) matched healthy comparison subjects lacking psychopathology. All subjects will be between the ages of 18 and 28 in order to minimize the potential confounds associated with developmental changes in oxytocin at puberty and with chronic mental illness. Healthy subjects will be included in order to test our hypothesis that oxytocin will have similar effects in both healthy subjects and patients with schizophrenia, and to verify that our paradigms are functioning similarly to previous studies in healthy subjects.

F.1.b. Inclusion/Exclusion Criteria: Exclusion criteria for both patients and healthy comparison subjects include meeting criteria for current substance abuse or dependence or illicit drug use within the last month (nicotine use is acceptable), any illness that affects the nasal passages and impairs the delivery of a nasal spray, and the presence of any neurological or significant medical disorder, including medical illnesses that could interfere with physiological recording such as cardiac arrhythmias. All subjects must pass a urine toxicology screen on each day of testing. Healthy subjects must not have had a current Axis I disorder within the last year and must not be taking any psychotropic medication or any medication that affects the autonomic or cardiovascular systems. Patients must have a SCID-IV confirmed diagnosis of schizophrenia or schizoaffective disorder with onset within the last 5 years, and be clinically stable (i.e. no significant change in clinical status or symptoms) and on a stable antipsychotic medication dose (i.e. no changes in medication or dosage) for at least the last 6 months. Patients must not be taking primary anticholinergic medications. Healthy controls will be matched to the patient population on age, education, body mass index and smoking habits.

F.1.c. Exclusion of Women: In the current studies, we will only recruit male patients with schizophrenia. We believe this is necessary for at least two reasons. 1) Oxytocin administration may have sexually dimorphic effects. For example, intranasal oxytocin decreases amygdalar responses to fearful faces in men[58] but appears to increase amygdalar responses to identical stimuli in women[78]. 2) The relationship between oxytocin responses, the menstrual cycle and sex remains unknown. For example, peripheral oxytocin levels are associated with emotion recognition abilities in both healthy and schizophrenic women but not in healthy or schizophrenic men[79] and peripheral oxytocin levels are associated with symptom severity in women but not in men with schizophrenia[20]. Given these unknowns in the relationships between sex, the menstrual cycle, oxytocin effects and schizophrenia, we believe that beginning to investigate the effects of oxytocin only in male patients will minimize inter-subject variability and maximize the feasibility of the current studies. However, we fully acknowledge that women are underrepresented as research participants and that the same research questions apply to a female population. Thus, follow-up studies to the proposed research will include women.

F.1.d. Screening and Determining Eligibility:

i) Medical Evaluation: Prior to participation in any study, participants will undergo a medical examination by a physician to ensure that there are no medical conditions that would contraindicate taking oxytocin or participating in the proposed studies.

ii) Diagnostic Evaluation: All potential participants will undergo the Structured Clinical Interview for DSM-IV (SCID), to establish the diagnosis of schizophrenia or schizoaffective disorder in the patient groups or to rule out the existence of Axis I disorders in the healthy control group. Interviews will be conducted by a doctoral-level clinician, and these interviews will be audio recorded and calibrated monthly with a senior clinician in the schizophrenia research program. Twenty percent of the interviews will be randomly selected and rescored by an independent clinical interviewer (senior clinician) to establish levels of inter-rater reliability. Threshold Kappas for Axis I diagnoses will be .80 and above. The Schizophrenia Team conducts weekly meetings for establishing diagnostic consensus, administrative meetings for tracking participant recruitment, and a study design and data review conference. Discrepancies that result from the evaluation of participants will be resolved by group consensus at these meetings.

iii) Completion of Questionnaires. Participants will complete self-report questionnaires on demographic information, health and psychological symptoms and current medications.

iv) Symptom Scales. Patients will also undergo symptom ratings evaluations (including the Positive and Negative Symptom Scale (PANSS)) and measures of social functioning (including a modified Quality of Life Scale (QLS), and the Social Functioning Scale (SFS)), within 1 month of participating in the proposed studies.

F.1.e. Subject Recruitment: Subjects will be outpatients recruited from: 1) The UCSF Prodromal Assessment Research and Treatment (PART) program, where Drs. Vinogradov and Mathalon are the Scientific Co-Directors, 2) The SFVAMC, where Dr. Vinogradov is the Interim Chief of the Mental Health Service; 3) The Langley Porter Psychiatric Institute (LPPI) of University of California, San Francisco, where Dr. Vinogradov is Professor and Interim Vice-Chair; 4) San Francisco Community Mental Health Clinics, where Dr. Vinogradov has extensive professional contacts; and 5) Various community clinical sites via referral from primary clinicians, use of brochures/fliers, and direct recruitment by the P.I. or his research assistants. In our preliminary studies involving intranasal oxytocin and two visits separated by a week, we have had zero drop-outs to date. However, in our experience recruiting patients with schizophrenia in this age-group, a conservative estimate of drop out (e.g., consenting and enrolling but then using substances, not showing up, decide not to do it, etc…) is 10%. Therefore, we will attempt to recruit 89 patients over the five-year study or roughly 18 subjects per year in order to recruit the 81 patients (or roughly 16 patients per year) that we require for the proposed studies. Given that the PART program alone recruited roughly 25 new patients with recent-onset schizophrenia (of which, two thirds were male) per year over the last three years, we will be able to meet our recruitment goals.

G. General Considerations:

G.1. Why Study Young Adults with Recent-Onset Schizophrenia?

Studying young adults with recent-onset schizophrenia provides an opportunity to study the disease without the confounds associated with chronic mental illness such as chronic social isolation, long-term medication exposure, progressive aspects of the illness pathophysiology, and non-specific aspects of chronic severe mental illness (e.g., poor nutrition, substance abuse, poverty and low socioeconomic status). Furthermore, it is unclear whether oxytocin dysfunction is a marker of the illness or a secondary consequence of the impoverished social interactions experienced by most schizophrenic patients for the majority of their lives. Therefore, it is crucial to examine oxytocin functioning early in the lives of affected patients, before they have become socially isolated. Additionally, early intervention has greater potential to alter the illness course before the patient's social and occupational functioning has severely deteriorated[80]. Finally, young adults with recent-onset schizophrenia may serve as ideal candidates for treatment with oxytocin because they often still have access to family, peer and school social support systems, which they may be able to maintain throughout their lives.

G.2. Dosage and Timing of Oxytocin Administration:

Vasopressin, a molecule similar to oxytocin, enters the cerebrospinal fluid within 10 minutes following intranasal administration, and levels continue to increase for at least 80 minutes[81]. Given the molecular similarity between oxytocin and vasopressin, we believe that oxytocin levels will remain high for several hours after intranasal administration. We have chosen the relatively high 40 IU dosage of oxytocin to minimize the possibility of Type II error. This dosage has been found to be safe and well tolerated in previous studies including one clinical trial in schizophrenia[7]. A delay of 40 minutes between administration of oxytocin and the initiation of testing was chosen for our studies because at this time, central nervous oxytocin levels reach a plateau[81] and healthy subjects show robust oxytocin-induced behavioral and physiological effects[3,46].

G.3. Peripheral Physiological Measure:

We have chosen Respiratory Sinus Arrhythmia (RSA) as our primary dependent variable given its putative link to the Social Engagement System (i.e., RSA is a latent measure of the Social Engagement System). Electrocardiography and respiration will be collected during the experiments and while subjects undergo fMRI. We will use Biopac hardware (ECG and RSP modules) and use CMetX and AcqKnowledge software packages to calculate RSA.

G.4. Eye-Tracking:

Subjects' eye-gaze patterns will be quantified in both proposed experiments. In Experiment 1, subjects' eye-gaze will be quantified using the Tobii X60. This device does not require any equipment be attached to the subject to track eye-gaze and allows for large head movements of the participants. For Experiment 2, subjects' eye-gaze will be quantified using a magnet compatible Long-Range Eye Tracking system from Applied Scientific Laboratories. For coding of eye-gaze**,** three *a priori* hotspot regions (the eyes, the nose and mouth, and the forehead and cheeks) will be created on each face. Measures will include eye-gaze duration (total time spent fixating on a hotspot) and fixation count (number of gaze fixations toward a hotspot region).

G.5. Timeline and Feasibility:

Time	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	
Duration of CDA award	◄	———	———	———	———	►
Experiment 1: Study enrollment and data collection	◄	———	———	►		
Aim 1 Data analysis Manuscript preparation		◄	———	———	►	
Aim 2 Data analysis Manuscript preparation			◄	———	———	►
Experiment 2: Study preparation (protocol, IRB etc) Study enrollment and data collection	◄	►				
Aim 3 Data analysis Manuscript preparation				◄	———	►

The rich resources available to this project at the SFVAMC and UCSF support the feasibility of recruiting adequate numbers of participants to successfully complete the objectives of this proposal. This includes study space, statistical support, and access to potential participants through collaboration with the outpatient mental health clinics and the research recruitment team. The Schizophrenia Research Program is located at the SFVAMC and is affiliated with UCSF and the Prodromal Assessment and Research Team (PART). These programs have many years of experience recruiting participants and conducting clinical research.

In addition, the PI has already established highly productive working relationships with his mentors, has navigated necessary regulatory bodies (IRB and FDA), has obtained significant experience administering intranasal oxytocin to patients with schizophrenia, and has successfully collected pilot data relevant to all three aims. This establishes his ability to carry out the proposed experiments in a timely and efficient manner. The Timeline for the experiments, data analyses, and manuscript preparation is outlined in the table above.

H. Potential Limitations and Plan to Address Them:

H.1. Antipsychotic Medications:

It is not feasible or ethical to study unmedicated patients with schizophrenia in the outpatient setting. We recognize, however, that antipsychotic medication status could confound the results of the present studies. In order to minimize the impact of this potential confound, only patients that have been on a stable dose of medication for at least six months will be included in our experiments. Furthermore, the within-subject design should minimize the effect of inter-subject variability. Additionally, because our goal is to improve social cognition and behavior in patients who are optimally treated with current evidence-based treatments including antipsychotic medications, it is important to study the effects of oxytocin on patients who are on “real-world” medication regimens. Relevantly, the one clinical trial of oxytocin in patients with schizophrenia demonstrated that oxytocin improved symptoms in patients who were also taking antipsychotic medications. Similarly, our preliminary data demonstrates that a single dose of oxytocin does indeed improve social cognition in patients with schizophrenia who are also taking antipsychotic medications. Finally, we will collect data on medication regimens and will explore any medication effects on the primary outcome measures.

H.2. Anticholinergic Effects:

Another potential issue is that patients are occasionally prescribed anticholinergic medications in order to minimize extra-pyramidal side effects of antipsychotic medications. Given that cholinergic signaling is present in PNS and preganglionic sympathetic nerves, anticholinergic medication could have strong effects on the autonomic measures in the current proposal. Therefore, patients taking primary anticholinergic medications will be excluded from the current study. Given that anticholinergic medications impair learning in patients with schizophrenia, in our clinical opinion they have little role in the treatment of schizophrenia. Only a small subset of patients (<20%) who are referred to our studies are on these medications. Furthermore, antipsychotic medications also have anticholinergic effects, which could confound the results from the current studies. However, the majority of patients with recent-onset schizophrenia who have participated in our previous studies have been on antipsychotic medications such as risperidone and aripiprizole, antipsychotics with no anticholinergic burden. While we cannot completely remove this potential confound, we will quantify and analyze the interactions between medication type and dosage and our primary outcome measures.

H.3. Symptom Variability:

One potential concern is that any effect of oxytocin in patients with schizophrenia will be dwarfed by variation in symptom severity both between and within subjects. However, we believe this will not be a major issue for three reasons: 1) We will only focus on clinically stable patients and in our experience these patients do not typically have significant symptom fluctuations over a single week. 2) We will use a within-subject design for all studies, which will minimize the impact of between-subject variability. 3) Our preliminary data show that oxytocin is having large significant effects on social cognition in patients with schizophrenia.

H.4. Order Effects:

While there are significant advantages to using a within-subject design, this design is sensitive to order and learning effects. Specifically, because subjects will undergo testing on two separate test days, there is a possibility that subjects will systematically change their performance from day to day. In our preliminary studies, we did not find any effect of order on social cognitive testing. We will test for order effects in all analyses and if significant order effects are found, order will be included in the analytic model.

Candidate's Background:

My research is focused on the neurobiological underpinnings of social behavior. As a physician scientist, I am particularly interested in uncovering clinically relevant neurobiological mechanisms of pathological social behavior that may eventually provide targets for intervention in psychiatric illness. Throughout my career, I have moved frequently between the clinic and research laboratory, often taking inspiration for methodologically sound scientific investigation from the careful observation of individual patients. This Career Development Award will provide me the opportunity to develop my program of research and to become an independent scientist within the VA healthcare system.

While obtaining my graduate and medical training at UCSF from 2000 to 2007, under the supervision of Drs. Howard Fields and Bruce Miller, I used human and animal model systems to pursue research on the neural substrates of palatability-driven choice behavior. While completing this work, I developed practical experience with laboratory-based animal research as well as clinic-based human research. In my laboratory research, I learned how to design and implement elegant pharmaco-behavioral experiments. In my clinical research, I studied patients with psychiatric and neurologic diseases as well as healthy individuals. In the process, I forged productive collaborations across disciplines and departments, gaining specialized training in neuropsychiatry, behavioral neurology and cognitive neuroscience.

More recently, during my clinical training as a psychiatrist, I learned to understand the subtleties of human behavior within a psychobiological framework. In particular, I recognized the terrible toll that social deficits take in patients with neuropsychiatric illnesses such as schizophrenia. This clinical insight in combination with my longstanding interest in the mechanisms of behavior, led me to focus my research on understanding social cognitive deficits in schizophrenia and in investigating the potentially therapeutic role of the pro-social neuropeptide oxytocin in ameliorating these deficits. I have already applied for and received a departmental grant, a UCSF Clinical and Translational Science Institute grant and a UCSF Treatment Research Center grant to support this research. Though early in my career as an academic research psychiatrist, I have developed a specific set of hypotheses that I plan to investigate via interdisciplinary research that bridges psychiatry, psychology and neuroscience and that involves translating basic science into clinically relevant applications. While I already have expertise in several scientific areas relevant to the proposed studies including clinical psychiatry and behavioral neuroscience, I require further training in functional neuroimaging, statistical analysis and psychophysiology in order to both successfully complete the proposed studies and to develop to my full potential as a research psychiatrist. Receiving the Career Development Award will provide me with the necessary training to help me transition into an independent scientist.

I am very familiar with and have a demonstrated dedication to the VA system and the care of mentally ill veterans. During medical school, I participated in a one-year clinical experience in an outpatient mental health clinic at the San Francisco Veterans Affairs Medical Center (SFVAMC). During residency, I spent six months working fulltime in the mental health service at the SFVAMC. For the last two years, I have been working closely with my primary mentor Dr. Vinogradov, the Interim Associate Chief of Staff for Mental Health at SFVAMC. During this time, my research has been primarily based at the SFVAMC and I am currently an Advanced Neuroscience Research Fellow at the SFVAMC. As part of my clinical duties, I currently act as a junior attending in an outpatient psychiatric clinic at the SFVAMC one day a week. Given that the **VA provides care to approximately 100,000 patients with schizophrenia each year, accounting for nearly 12% of the VA's total healthcare costs**, the VA system is an ideal place for me to develop my research and clinical interests focused on schizophrenia. Finally, I enjoy working within the VA medical system due to the comprehensive clinical resources available and its focus on preventative medicine seldom seen in other clinical settings. In sum, I am dedicated to developing into a clinical scientist working within the VA health system and focusing my research on veteran-relevant health issues.

My goal in seeking this Career Development Award is to acquire the training, practical experience, and knowledge necessary to become a leading independent clinical investigator in the field of social neurobiology. Specifically, I require further training in: 1) functional neuroimaging; 2) statistical analysis; and 3) psychophysiology, in order develop to my full potential as an independent researcher.

1) While I have expertise in the analysis of structural imaging, neuroimaging techniques such as fMRI

are the gold standard research tool for understanding the brain's processing of social information as they allow for strong spatial and temporal resolution of task related brain activity. Stimulus design, testing procedures, and image processing and analysis are critical techniques for me to master as a neuroscientific investigator.

2) Despite my clinical training and experience in research design and implementation, I do not have a sufficient level of knowledge about advanced statistical techniques to attain many of my goals as an independent investigator. For example, because I was studying animal behavior in well-controlled laboratory paradigms utilizing randomized designs that minimized confounding, the statistics that I utilized in my graduate work were simple t-tests and ANOVAs. However, my more recent work in clinical research settings has demonstrated for me that I will need to become proficient at analyzing data sets from clinical populations with multiple potentially confounding variables and multiple predictors of interest, as well as more advanced regression techniques requiring multi-predictor, mixed, and hierarchical modeling. Therefore, in order to obtain the skills necessary to maximize my effectiveness as an independent investigator in the field of human social neurobiology, it is critical for me to acquire training in advanced statistics.

3) I have never before utilized psychophysiological methods in my investigations. This is a critical gap in my training as the physiological signals associated with emotional states can be used to investigate affective processing in ways that purely behavioral outcomes cannot. In other words, behavioral outcomes are often too crude a measure to detect the subtle changes that are happening "under the skin" that are so important to emotional experience. By adding psychophysiological techniques to my research armamentarium, I will be able to investigate social neurobiology at a deeper and more fine-grained level of analysis. This will be important for my development into an independent researcher.

My overall career goal is to develop novel therapeutic interventions for social deficits in multiple patient groups and to use multiple techniques including neuroimaging to explore the mechanisms of these deficits. I propose to investigate the role of the neuropeptide oxytocin in social dysfunction in schizophrenia using pharmacological, neuroimaging, behavioral and psychophysiological techniques. Specifically, in patients with recent-onset schizophrenia, I will examine the effects of oxytocin on: (1) social cognition, attention to others' eyes, and facial and vocal affect expressivity; (2) parasympathetic nervous system (PNS) activity; and (3) neural activity during processing of social stimuli.

Career Goals and Objectives:

Past Scientific History: I have been fascinated by the conscious and unconscious mind since childhood, and have dedicated my career to exploring the mind and elucidating determinants of behavior. These passions led me to pursue a joint MD/PhD and psychiatric training with a view to combining clinical practice and academic research as a research psychiatrist. To date, my work has spanned basic neuroscience and clinical research, using diverse methods to uncover the neural substrates of behavior.

As a graduate student, I investigated the neurohormonal underpinnings of compulsive overeating in patients with frontotemporal dementia (FTD) using behavioral, hormonal and structural imaging techniques in the laboratory of Dr. Bruce Miller (Woolley et. al., 2004; Woolley et. al., 2007a). Simultaneously, I conducted studies investigating the role of ventral striatal opioid signaling in feeding behavior in rats in the laboratory of Dr. Howard Fields (Woolley et. al., 2006; Taha, Norsted, Lee, Lang, Lee, Woolley, and Fields, 2006; Woolley et. al., 2007b, Woolley et. al., 2007c). During my clinical training, I published several case reports of well-characterized patients with uniquely illustrative presentations (Woolley, et. al., 2007d; Woolley et. al., 2010; Khan, Woolley, et. al., 2011). I also completed a large retrospective study of patterns of psychiatric misclassification of patients with neurodegenerative disease (Woolley et. al., 2010) as well as a study investigating BDNF levels in patients with neurodegeneration (Woolley et. al., 2011).

While working with patients with FTD for my PhD thesis, I became aware of the profound impact of disease-related social skills deficits on patients' quality of life. Later, during my clinical training, I was struck by the important role social support plays in recovery from psychiatric disorders and the toll that symptoms of many psychiatric disorders take on social relationships. As a physician, I had few treatment options to address these symptoms and often wished I could "prescribe" a friend to my patients. Thus, after some careful

thought, I decided to marry my passions for neuroscientific research and clinical practice by focusing my program of research on the neuroscience of social behavior with the ultimate goal of developing novel treatments to improve quality of life in patients with neuropsychiatric disorders. I also realized that schizophrenia would be an ideal disorder in which to begin examining some of my developing hypotheses because it was clear that these patients' profound social deficits isolate them from important sources of social support.

Career Goals: My long-term goals are to pursue an academic career in psychiatric neuroscience within the Veterans Affairs health system, incorporating insights from the bedside and performing clinical and basic research. I hope to use breakthroughs from behavioral neuroscience in animals and insights from clinical experience to inform my behavioral, cognitive and nuerophysiological research on social behavior in patients. My research will focus on neurohormonal and behavioral aspects of social relationships and cognition. While the current studies are focused on schizophrenia, I envision this work having implications beyond psychotic disorders. Eventually, I hope to apply the skills and knowledge gained through the successful completion of these studies to the investigation of neurohormonal mechanisms of social dysfunction in patients with substance abuse and post-traumatic stress disorders.

Training Activities During Award Period

During the period supported by this Career Development Award, my research objectives are to develop a greater understanding of the neurohormonal mechanisms of disrupted social behavior in patients with schizophrenia. In order to establish myself as an independent investigator and accomplish these goals, I have identified three major areas in which I will build my expertise with intensive study: 1) fMRI techniques; 2) advanced statistical analysis including advanced regression techniques such as multi-predictor, mixed, and hierarchical modeling; and 3) the methods, theory and data analysis techniques for studies of psychophysiology. I will expand upon my training plans in these areas including formal coursework, seminars, conferences and mentoring opportunities below.

1) Neuroimaging Techniques: A major focus of my training will be to learn about functional neuroimaging modalities and their use in clinical studies. This will involve acquiring knowledge about the basic principles of MRI physics and their impact on neural activity and functional connectivity using approaches such as event-related and resting state imaging. These techniques are distinct from those that I have already learned to investigate brain-behavior correlations through the analysis of structural brain images. I will learn the use of state-of-the-art imaging software such as Statistical Parametric Mapping (SPM) that provide quantitative assessment of brain images through coursework and one-on-one mentoring from Dr. Mathalon who is an expert in neuroimaging investigations in patients with schizophrenia. I will then apply these skills and knowledge to the successful completion of Experiment 2.

Course Work:

Medical Imaging Informatics. 170.03 Department of Biological & Medical Informatics, UCSF. Instructor*(s):* K. Young, N. Schuff. This course focuses on teaching modern techniques for the analysis of multi-parametric medical imaging data, including structural, functional, and spectroscopic imaging. This class will introduce me to modern methods for processing and analyzing large volumes of heterogeneous data with a specific focus on MRI data and will provide me the knowledge and skills necessary to analyze the data from my neuroimaging experiments.

Short course on Statistical Parametric Mapping for Functional Neuroimaging. Wellcome Trust Centre for Neuroimaging, University College London. This three-day course, which has been held annually since 2007, offers comprehensive coverage of all MRI-related aspects of SPM, including spatial preprocessing, voxel-based morphometry, mass-univariate and multivariate analyses of fMRI data, Bayesian analysis methods, Dynamic Causal Modeling and Bayesian Model Selection. This course will give me necessary experience in using statistical methods for image analysis and interpreting the results using the SPM software package.

2) Statistical Analysis: In order to successfully complete the proposed studies and to develop into an independent researcher, I will need to broaden my skills in statistical analysis. In addition to one-on-one mentoring from Dr. Rankin, who has extensive experience in research design and statistical analysis in quasi-experimental and observational clinical research settings, as well as in analysis of randomized experimental designs requiring multivariate modeling, I plan to attend courses in statistical techniques such as advanced regression techniques and a course focused on advanced analysis techniques for neural and behavioral data. Then, through hands-on application of these skills to data produced from Experiments 1 and 2 in close apprenticeship with Dr. Rankin, I will further develop my statistical expertise.

Course Work:

Introduction to Linear Models, 192, Course Director: Division of Biostatistics, UCSF. Course Director: Steve Paul, PhD. This course begins with bivariate correlation and simple linear regression and then moves on to a presentation of multiple regression techniques and the analysis of variance under the general linear model. It will focus on designs involving a quantitative dependent variable and independent variables of either a quantitative or categorical nature. In this course, I will learn about choice of analytic techniques and interpretation of results. This experience will be a critical first step for me to develop my statistical skills and knowledge.

Biostatistical Methods for Clinical Research III. 209 Division of Biostatistics, UCSF. Course Director: John Kornak, PhD. This course covers multi-predictor methods, including exploratory data analysis, multiple regression (linear and logistic) analyses, survival analysis and repeated measures analysis. I will learn the practical and proper use of statistical methodology and the interpretation of advanced statistical methods. This course will allow me to further develop my knowledge of statistics and will provide me the necessary skills to successfully analyze my data.

Analysis of Neural and Behavioral Data. 248 Department of Neuroscience, UCSF. Course Director: Loren Frank, PhD. This course will provide me with an in-depth introduction to methods and techniques used for the analysis of neural and behavioral data. The following topics will be covered in the course: probability and probability distributions, descriptive statistics for gaussian and non-gaussian data, regression, auto and cross correlations, reverse correlation, information theory and likelihood based model building for both neural and behavioral data using the MATLAB programming platform. This course will provide me with critical practical skills and theoretical knowledge for the analysis of the data produced during this Career Development Award.

3) Psychophysiology: While I have extensive training in the clinical assessment and treatment of psychiatric illness, basic neuroscientific principles and human physiology, I need to develop greater expertise in psychophysiology including data collection and analytic methodologies. This training will both improve the design and implementation of my studies and increase the quality and scientific impact of my research. In addition to one-on-one mentoring meetings with Dr. Mendes, who is a world expert on autonomic nervous system monitoring and has extensive experience with multivariate analyses, time series, and multi-level modeling, I will participate in relevant seminars and learn from the practical application of these skills through the completion of the proposed Experiments 1 and 2.

Seminars:

Social Deficits and Remediation in Schizophrenia Journal Club. SFVA. Facilitator: Josh Woolley MD/PhD (PI). This is a bi-monthly journal club attended by physicians, staff scientists, postdoctoral scholars, and research assistants, which I started in June of 2010 and lead with the help of Sophia Vinogradov (Mentor). At each meeting we review a recent article that is broadly relevant to the neurobiology and treatment of social behavioral deficits in schizophrenia. Attending and leading this journal club both helps me stay abreast of recent relevant research and provides me an opportunity to develop my leadership and teaching skills.

Topics in Social Psychology and Psychophysiology. Langley Porter Psychiatric Institute, UCSF. Course Director: Wendy Mendes PhD (Co-Mentor). This is a weekly journal club and

discussion group led by Dr. Mendes where investigators from multiple disciplines including psychology, psychiatry, and neuroscience take turns presenting relevant journal articles, preliminary data and new study ideas. Topics include the design and analysis of social psychological studies as well as quantitative methods for evaluation of psychophysiological responses including topics in advanced statistics such as multi-level modeling, structural equation modeling, and dyadic data analysis. This seminar will allow me to further develop my knowledge and skills in social psychology and psychophysiology.

Conferences:

World Congress on Neurohypophysial Hormones. This yearly meeting has the stated goal of bringing "together experimental and clinical scientists from all over the world to focus on recent advances in the molecular biology, physiology, and neurobiology of vasopressin and oxytocin and their ancestral peptides in non-mammalian vertebrates." In other words, this meeting focuses on oxytocin relevant research. I will attend this meeting each year of the award. This experience will allow me to continue to develop my knowledge of cutting edge research in oxytocin biology and applications, and will also allow me to start developing critical international collaborative relationships with leading figures in the field.

Practical Research Training: Through conducting the proposed research, I will learn to independently manage clinical studies, particularly pharmacological and neuroimaging studies in schizophrenia. By conducting Experiment 1, I will gain mentored practical experience in the conduct of a pre-clinical laboratory based pharmacological study including protocol development, IRB approval, recruitment, study coordination and database management as well as methodologies for the assessment of social cognition, eye-gaze and psychophysiology. By conducting Experiment 2, I will gain practical experience with all aspects of directing a functional neuroimaging study. Furthermore, "hands-on" work with the help of experienced technicians from the Neuroimaging Center (NIC) at UCSF will give me practical experience with quality assessment and image processing. Together, these experiences will allow me to apply for independent funding for large-scale studies in the second part of the award period.

Clinical Training: During my clinical/teaching time I will see psychiatric patients with recent-onset schizophrenia at the SFVAMC to keep my psychiatric expertise up-to-date and to gain further experience with the management of this disease. I will be trained in clinical assessment and evidence-based treatments including cognitive behavioral therapy for psychosis and advanced pharmacotherapy. During this clinical/teaching experience, I will also work closely with and mentor psychiatry residents at UCSF. This will allow me to further develop my teaching and supervision skills, which will be critical for my career as an academic research psychiatrist.

	Year 1	Year 2	Year 3	Year 4	Year 5
Formal Coursework	←	→			
Seminars	←	—	—	—	→
Mentored apprenticeship: neuroimaging	←	—	—	—	→
Mentored apprenticeship: statistics	←	—	—	—	→
Mentored apprenticeship: psychophysiology	←	—	—	—	→
VA Merit preparation & submission				←	→
Clinical responsibilities and teaching	←	—	—	—	→

Training in the Responsible Conduct of Research: In 2003, I completed a course entitled "Responsible Conduct of Research" as part of the UCSF Clinical and Translational Research Program. This course is designed to address the requirements of the National Institutes of Health for the education of investigators about ethical issues in research involving human subjects. I have also completed on-line training courses required by the Veterans Affairs Medical Center on research involving human subjects. I will maintain up-to-date certification throughout the award period. Furthermore, I will discuss practical issues in research ethics in my regular mentor meetings.

My training in neuroscience, neurology, and clinical and research psychiatry provides a solid foundation for the proposed studies. However, to successfully complete the proposed studies and to develop into a successful independent researcher, I require mentorship in several key domains. First, I require mentorship in developing and managing a program of research, leading a research group, and applying for independent funding. Second, I require mentorship as I develop the skills outlined in my training plan. These include: 1) Specific research methods in functional imaging techniques, such as task related and resting state fMRI methodologies; 2) Statistical analysis of data from behavioral experiments in clinical populations; and 3) Psychophysiological measurement and analysis techniques. Additionally, while I have a strong background in basic neuroscientific principles and human physiology, I need to further develop my expertise in oxytocin biology in order to enhance the quality and scientific impact of my studies. In sum, I will learn how to design, implement and analyze experiments investigating neurophysiological, behavioral, and psychological factors underlying social behavior in patients with psychiatric illness. In order to achieve this goal, I have assembled a multidisciplinary mentoring team who will provide the expertise and guidance necessary for me to succeed with my research plan and career objectives. All are senior NIH funded investigators who are world leaders in their areas of research. I will meet in person with each of my mentors at least bi-weekly. Further, thrice a year, all of my mentors and I will meet as a team to discuss my progress. In addition, I will have contact with my consultants on an as-needed basis, and through quarterly phone meetings and yearly in-person meetings.

Primary Mentor: Sophia Vinogradov, MD: My primary mentor is Dr. Vinogradov, who is the Interim Associate Chief of Staff for Mental Health at the SFVAMC, as well as a Professor in Residence of Psychiatry and Interim Vice-Chair of the Department of Psychiatry at UCSF. She is a world expert in cognitive training in schizophrenia and has extensive clinical and research experience working with patients with schizophrenia. She will supervise me on all aspects of the proposal (Aims 1-3), career development, as well as manuscript and grant preparation.

Dr. Vinogradov's work focuses on harnessing the plasticity of dysfunctional neural systems through neuroscience-guided computerized training programs. She currently holds three R01 grants from NIMH, one that focuses on behavioral, MEG, fMRI, and serum biomarker correlates of the effects of a translational "neuroplasticity-based" cognitive training program in schizophrenia, one that focuses on an adaptation of this approach to prodromal adolescents, and another that focuses on a trial of another adaption of this approach specifically targeting the social cognitive deficits in schizophrenia. Dr. Vinogradov also holds an SMRI grant for a controlled trial of computerized training in recent-onset schizophrenia. Through studies like these, Dr. Vinogradov has extensive experience and expertise in multidisciplinary investigations in patients with schizophrenia. Dr. Vindogradov has also served on the National Task Force for Psychiatry Research Training, led by Dr. John Greden, and has extensive mentoring experience with previous mentees achieving academic positions in leading institutions.

Through weekly meetings with Dr. Vinogradov, I will develop expertise in designing, implementing and analyzing experimental studies with clinical populations suffering from severe psychiatric illness. I will meet individually with Dr. Vinogradov every week and we will review methodological and conceptual issues relating to my ongoing research as well as hypothesis development and data analysis. As appropriate, these meetings will focus on the preparation of manuscripts for publication. Dr. Vinogradov will supervise my overall progress and will be involved in all aspects of the proposed research. She will also provide guidance and supervision as I develop organizational skills for running complex multivariate studies and leadership skills for successfully managing a research team. I will also participate with Dr. Vinogradov and other members of the laboratory in weekly Data Meetings (review of data management, acquisition, reduction and analysis). During the last two years of the award period, I will also work with Dr. Vinogradov on applications for extramural funding as an independent investigator to continue my research.

Co-Mentor: Daniel Mathalon, PhD/MD: Dr. Mathalon, Associate Adjunct Professor of Psychiatry at UCSF and SFVAMC, is an expert in neuroimaging techniques in patients with schizophrenia and will serve as the mentor for the neuroimaging portion of this award (Experiment 2). He is the Director of Neuroimaging of the Prodromal Assessment, Research, and Treatment (PART) program at UCSF. He also collaborates with other faculty by applying his fMRI expertise to other disorders including compulsive hoarding, post-traumatic stress disorder, chronic pain, and treatment-resistant depression. Dr. Mathalon has research funding from NIMH and the NARSAD foundation. For the past two years, he has served as Director of the Resident Research Track at UCSF, facilitating the recruitment and training of psychiatry residents interested in pursuing research careers.

Dr. Mathalon is a trained clinical psychologist and psychiatrist whose research uses EEG, event-related

potentials, and fMRI to study the pathophysiology underlying the symptoms and course of schizophrenia. A major focus of his research is to identify neurophysiological markers of risk for psychosis that can improve our ability to predict which patients at clinical high risk for psychosis will go on to convert to a full-blown psychotic disorder. He has mentored numerous psychiatry residents and psychology fellows over the past decade, with many of his mentees successfully competing for NARSAD grants and securing faculty positions in psychology or psychiatry departments around the country. Given his expertise in neuroimaging techniques and his extensive mentoring experience, Dr. Mathalon is perfectly suited to mentor me on the neuroimaging components of this proposal.

Dr. Mathalon has already mentored me in two capacities. First, during my time as a research track resident, he was always readily available to discuss professional development issues and he provided excellent feedback on grants and manuscripts. More recently, Dr. Mathalon has started mentoring me on the analysis of functional neuroimaging data, which will continue into the award period. In particular, I will continue to meet bi-weekly with him to discuss methodological and conceptual issues concerning the use of task-related fMRI in patients with severe mental illness. During our meetings, we will discuss methods and data related to Experiment 2. Dr. Mathalon will also monitor and guide my development as a neuroimaging researcher.

Co-Mentor: Wendy Berry Mendes, PhD: Dr. Mendes holds the Sarlo-Ekman Chair in Human Emotion Research, and is an Associate Professor in the Department of Psychiatry at UCSF. She will be the primary mentor for all aspects of the study that involve psychophysiology (Aims 1-3). She is the founder and director of the Emotion, Health and Psychophysiology Laboratory at UCSF, which conducts basic and translational research with healthy and clinical populations. With clinical populations, she draws on affective science research to inform studies of psychopathological processes in depression, anxiety disorders and self-harm. Her research also focuses on social and psychological processes stemming from perceptions and experiences of discrimination and stigmatization. Her work has been acknowledged with several career awards including the Society for Personality and Social Psychology Sage Early Career Award (2009), the Gordon Allport Award for best paper on intergroup relations (2008), and the Association of Psychological Science Janet Taylor Spence award for transformative early career contributions (2011).

Methodologically, Dr. Mendes incorporates neuroscience and biological measures to investigate underlying affective states in human interactions. Her primary expertise includes autonomic nervous system monitoring, as well as electromyography, electroencephalography, and electrogastrography. She holds annual training workshops in psychophysiological assessment at UCSF that are attended by researchers from across the country. Dr. Mendes holds a degree in quantitative psychology and coordinates statistical workshops on multivariate analyses, time series, and multi-level modeling. She has extensive experience mentoring graduate and post-doctoral students at UCSF and in the Psychology Department at Harvard. As core faculty in the Robert Wood Johnson Health and Society Fellows program at Harvard, she supervised two fellows, and has directly supervised 6 additional post-docs (two NRSA, two with foundation funding and 2 with grant funding). One is still a fellow and the remainder are all in assistant professorships, as are three doctoral students whom she supervised, with a fourth in post-doctoral training. Given her expertise in the use of psychophysiological measures to investigate affective states as well as her excellent mentoring track-record, she is an ideal person to mentor me on the proposed studies.

I first came in contact with Dr. Mendes when she started at her position at UCSF in the Fall of 2010 and since that time we have been meeting regularly. Dr. Mendes will serve as the primary mentor for the psychophysiological sections of the proposed award and will also provide supervision on statistical analysis. Through bi-weekly meetings with Dr. Mendes, I will develop expertise in the design, implementation and analysis of psychophysiological experiments. During these meetings, we will discuss methodological and conceptual issues related to psychophysiological experiments including task design, physiological modality selection and recording, and statistical analysis of multi-channel, time series data. In particular, Dr. Mendes will provide guidance on data acquisition and analysis of autonomic data for Experiments 1 and 2.

Co-Mentor: Katherine Rankin, PhD: Dr. Rankin is an Associate Professor in the Department of Neurology at UCSF, and is P.I. of the Data and Biostatistics cores on a multi-site NIH program project grant at the UCSF Memory and Aging Center. She is a leading expert on the neural substrates of social behavior in neurodegenerative disease and has extensive skill in both the measurement of social cognition and behavior and in the statistical analysis of social data from patient populations. She will serve as the primary mentor for my training goal of acquiring advanced statistical knowledge and will provide guidance on the measurement and analysis of social cognition in Experiment 1 of the proposed studies.

Dr. Rankin's research focuses on developing and validating measures of social cognition in frontotemporal dementia and other neurodegenerative diseases, with a particular interest in examining the neuroanatomic correlates of social functioning. Her training in behavioral neurology and expertise in quantitative analysis of neuroanatomy has allowed her to develop and implement novel statistical approaches to investigating the neuroanatomy of social cognition. She is an expert in designing, validating, implementing, and analyzing tests to measure complex aspects of social cognition in patients with cognitive deficits. As such, Dr. Rankin was part of the group of international leaders who recently established the new criteria for the diagnosis of behavioral variant frontotemporal dementia. Dr. Rankin has published many papers for which she personally performed advanced analyses using statistical techniques such as mixed modeling, discriminant function analyses, and multi-predictor modeling. Dr. Rankin mentors both M.D. and Ph.D scientists in statistical methods and research design and has successfully mentored nine post-doctoral fellows and two junior faculty members over the past 4 years. Her expertise in the assessment of social cognitive deficits in patient populations as well as her extensive experience in using advanced statistical methods to analyze data from these assessments will prove invaluable for the successful completion of the proposed studies as well as for my development into an independent researcher.

I have had a very productive working relationship with Dr. Rankin for the past seven years, coauthoring six articles over this time, though we have only recently begun to perform the more advanced statistical techniques for which I have chosen to obtain her mentorship. During the award period, I will meet weekly with Dr. Rankin to discuss study design and implementation, data acquisition and analysis, statistical principles and manuscript preparation. The goal of our continued work will be for me to develop greater independence in selecting and programming complex multi-predictor and longitudinal statistical models.

Consultant: Sue Carter, PhD: Dr. Sue Carter is a Professor of Psychiatry and the Co-Director of the Brain Body Center, at the Department of Psychiatry, at the University of Illinois at Chicago as well as the former president of the International Behavioral Neuroscience Society. Dr. Carter is an internationally renowned expert in oxytocin biology, animal models of attachment and behavioral neuroendocrinology. She pioneered the physiological study of socially monogamous mammals, including the prairie vole, and was the first person to identify the physiological mechanisms responsible for social monogamy. Her work is the foundation for studies of the behavioral and developmental effects of oxytocin in humans and has been recognized by numerous awards including the J. W. Fulbright, Distinguished Alumni Award, from the University of Arkansas and the Wayner-NNOXe Pharmaceutical Award for Translational Research, awarded by the International Behavioral Neuroscience Society. I have already established a mentoring and collaborative relationship with Dr. Carter. I will speak with her by phone on an as needed basis to discuss conceptual issues concerning the underlying biology and physiology of neuropeptides in attachment and social behavior. I will travel to Chicago to meet with Dr. Carter yearly and will keep her abreast of my progress at least quarterly by email and phone.

Consultant: Stephen Porges, PhD: Dr. Stephen Porges is a Professor of Psychiatry and Co-Director of the Brain-Body Center at the University of Illinois at Chicago. He is a world-expert in the evolution and functioning of the autonomic nervous system and how the functioning of this system relates to social behavior. His work forms much of the theoretical foundation for my proposed studies. His Polyvagal Theory links the evolution of the autonomic nervous system to the emergence of social behavior. He was also the first to quantify and use heart rate variability both as a response and individual difference variable in psychophysiological research, and he introduced respiratory sinus arrhythmia as an index of vagal function. He was also awarded a patent on a methodology to describe neural regulation of the heart. I will speak with him by phone on an as needed basis to discuss conceptual issues concerning underlying autonomic physiology and neuroanatomy as well as methodological issues concerning quantification and analysis of physiological data. I will travel to Chicago to meet with Dr. Porges yearly and will keep him abreast of my progress at least quarterly by email and phone.

Consultant: David Leitman, PhD: Dr. Leitman is an Assistant Professor in the Department of Psychiatry at the University of Pennsylvania. He is an expert in the study of vocal emotion as conveyed through intonation change (prosody) in neuropsychiatric illness. His research employs multiple methodologies including psychophysics, neuropsychology, EEG and functional and structural MRI, to investigate how vocal affect signal transmissions are coded, the channels used for such coding, and the receiver's ability to process such signals. I have been collaborating with Dr. Leitman for the last year and will continue to consult with him by phone on an as needed basis to discuss conceptual and methodological issues concerning the investigation of prosodic processing in patients with schizophrenia. I will keep him abreast of my progress at least quarterly by phone.

Risk to Subjects.

Human Subjects Involvement and Characteristics.

We will recruit 81 (45 for Experiment 1 (Aims 1 and 2) and 36 for Experiment 2 (Aim 3)) male young adult patients with a recent-onset psychotic disorder and 81 (45 for Experiment 1 (Aims 1 and 2) and 36 for Experiment 2 (Aim 3)) matched healthy controls lacking psychopathology. All subjects will be between the ages of 18 and 28 in order to minimize the potential confounds associated with developmental changes in oxytocin at puberty and with chronic mental illness. Healthy controls will be included in order to test our hypothesis that oxytocin will have similar effects in both healthy controls and patients with schizophrenia, and to verify that our paradigms are functioning similarly to previous studies in healthy subjects.

Inclusion/Exclusion Criteria:

Exclusion criteria for both patients and controls include meeting criteria for current substance abuse or dependence or illicit drug use within the last month (nicotine use is acceptable), any illness that affects the nasal passages and impairs the delivery of a nasal spray, and the presence of any neurological or significant medical disorder, including medical illnesses that could interfere with physiological recording such as cardiac arrhythmias. All subjects must pass a urine toxicology screen on each day of testing. Healthy subjects must not have had a current Axis I disorder within the last year and must not be taking any psychotropic medication or any medication that affects the autonomic or cardiovascular systems. Patients must have a SCID-IV confirmed diagnosis of schizophrenia or schizoaffective disorder with onset within the last 5 years, and be clinically stable (i.e. no significant change in clinical status or symptoms) and on a stable antipsychotic medication dose (i.e. no changes in medication or dosage) for at least the last 6 months. Patients must not be taking primary anticholinergic medications. Healthy controls will be matched to the patient population on age, education, body mass index and smoking habits. Subjects will include veterans and non-veterans. Non-veterans will be included because it is not feasible to recruit adequate numbers of veterans in this age range with recent-onset schizophrenia within the study time frame. Based on our experience, the clinical characteristics of a non-veteran sample of patients with recent-onset schizophrenia will be nearly identical to those of a veteran sample, allowing the findings to be generalized to the clinical features and needs of veterans. Those who have metal in their bodies for medical reasons such as a pacemaker or metal prostheses will be excluded from Experiment 2 (Aim 3).

Sources of Materials. Not applicable.

Potential Risks.

Oxytocin

The potential risks to subjects that participate in these studies are minimal. Side effects of intranasal oxytocin include a runny, stuffy, or irritated nose as well as very rare nausea and vomiting. However, oxytocin has been administered intranasally to thousands of individuals and no serious adverse effects have been documented at the dosages used in the current study (Macdonald 2011). Furthermore, in our preliminary studies, there have been no side effects noted for intranasal oxytocin.

Physiologic Sensors

The sensors that are used to measure physiologic parameters also have minor side effects. They are similar to adhesives used in band-aids. They are non-invasive and not

painful. Some people experience minor epidermal redness or irritation upon removal of the sensors, which generally goes away within an hour.

Fatigue
Participants may experience anxiety and/or fatigue during the assessments due to the length of the study and the time spent looking at a computer screen.

fMRI
The fMRI scanning may elicit some anxiety because scanning requires that participants be enclosed in a small space, and some participants may find it uncomfortable. The MRI scanner is also loud, and some participants may be bothered by it. Finally, implanted metal medical devices may malfunction or cause problems during a scan.

Data
Another potential risk is the loss of confidentially as a result of the identifying, descriptive, and clinical data obtained. Videotaping of participants during study tasks increases the risk that confidentiality and privacy may be compromised given the identifiable nature of video contents.

Adequacy of Protection from Risk
Recruitment and Informed Consent.
Subjects will be recruited from: 1) The UCSF Prodromal Assessment Research and Treatment (PART) program, where Dr. Vinogradov is the senior Director, 2) The SFVAMC, where Dr. Vinogradov is Associate Chief for Research and Education on the Mental Health Service; 3) The Langley Porter Psychiatric Institute (LPPI) of University of California, San Francisco, where Dr. Vinogradov is Professor; 4) San Francisco Community Mental Health Clinics, where Dr. Vinogradov has extensive professional contacts; and 5) Various community clinical sites via referral from primary clinicians, use of brochures/fliers, and direct recruitment by the P.I. or his research assistants.

Most of the subjects for the currently proposed studies will have already participated in other studies at our center and will have consented to be contacted for further research. These subjects will be contacted by phone by key personnel of the current proposal and asked about their interest in participating in our study. All other potential subjects will contact us after seeing various recruitment materials including flyers, dear doctor letters and craigslist ads.

Qualified, trained, key personnel will discuss the study with potential participants over the telephone and in person and conduct an initial eligibility screen. If eligible, subjects will be scheduled for an intake visit where signed, informed consent will be obtained in person in accordance with Committee on Human Research guidelines and approval. Subjects will be given as much time as necessary to consider study participation.

Protection Against Risk
If subjects become uncomfortable during any part of a study, they may decline to do any set of tasks or withdraw from the study entirely. The PI, co-PI, and co-investigators will be available to all subjects, family members, and clinicians for any concerns that arise regarding the study.

Oxytocin

To minimize the risk of oxytocin side effects and discomforts, study participants will be closely monitored for any adverse reactions to the intranasal administration of oxytocin. The proper usage of an intranasal device will be demonstrated and explained to participants who may not be familiar with this type of drug administration. A medically licensed physician will be available throughout all studies. Although the risks associated with intranasal oxytocin use are minimal, all study participants will be monitored for any physical side effects and will be provided with rest, a drink of water or a snack, or the option to discontinue the study should any side effects occur. 40 IU dosage of OT has been used in previous studies and found to be safe and well tolerated (MacDonald E 2011).

Physiologic sensors
If subjects experience any discomfort such as redness or itching at the site of the adhesive physiologic sensors at any point during the study, we will remove them.

Fatigue
Subjects will be encouraged to take breaks as necessary during assessments to alleviate fatigue. We will monitor nonverbal signs of fatigue and inquire about how the subject is feeling during the assessment at regular intervals to minimize any strain they may be experiencing. Any time the subject experiences undue strain or fatigue, the procedures will be halted and another time of evaluation can be scheduled. Any time a subject becomes agitated, the testing will be stopped and a clinician will be available to talk to him or her.

fMRI
Participants will be asked to remove all metal items from their body in Experiment 2 (Aim 3). If the participant has metal within their body such as a pacemaker or metal prostheses, they will be excluded from the study. Participants will be closely monitored for any signs of discomfort and will be offered earplugs if the noise of the MRI scanner is uncomfortable. If subjects become agitated or upset by the scanning procedure, they will immediately be removed from the scanner and testing will stop.

Data
Data are coded, kept in a locked file cabinet, and kept in a locked office in which the data key is kept separately and securely. Electronic data are password protected and stored on the secure VA network. Identifiers including protected health information will be kept in locked cabinets of locked office areas when not directly in use by key personnel. All electronic data will be stored on VA computers with anti-virus software, and password protection systems. Videotapes recorded during testing will be saved on password protected computers. Recordings will only be viewed by researchers involved in the study to examine facial expressions. All lab staff at SFVA and UCSF, regardless of employer and funding source, must complete a training and registration process with the hospital before beginning to work in the lab. This process includes privacy education and training which must be renewed annually.

Potential benefits of research to subjects and others

Benefits for subject
There are no direct benefits to patients beyond payment to participate. However, the risks associated with participation in this study are minimal and thus are acceptable considering the value of the knowledge obtained and the potential benefits to society.

Benefits for society

The results of this study may provide significant insight into future beneficial oxytocin treatments for social deficits in schizophrenia especially in the early stages of the illness. Ultimately, this information may lead to improved outcomes above and beyond what is currently available through standard treatments. If oxytocin administration remediates social deficits in schizophrenia in this preclinical study, this will support performing larger clinical trials of oxytocin in this patient group.

Data and Safety Monitoring Plan

In order to safeguard the well-being of all subjects enrolled in our study, each subject will be monitored for the following:

a. Adverse Event: Any untoward medical occurrence in a subject that does not necessarily have a causal relationship with the assessment procedures. This will include any unfavorable and unintended clinical sign, symptom, or illness temporally associated with the use of the assessment, whether or not considered related to it.

b. Serious Adverse Event: Any adverse experience that results in any of the following outcomes: death, a life threatening experience, acute psychiatric decompensation, inpatient hospitalization, or a persistent or significant disability/incapacity.

c. Unexpected Adverse Event: Any adverse experience the specificity or severity of which is not consistent with the risks information described in this study protocol or consent/assent documents.

The PI (Dr. Woolley) will be notified whenever an Adverse Event occurs. The PI will consult with the research staff, subject, his/her family and healthcare providers in formulating a plan for care (if necessary), then notify the UCSF and SFVAMC Committees on Human Research of the Adverse Event. The PI will comply with the recommendations of the CHRs as regards any necessary actions to take in response to the Adverse Event. Thus, all serious and unexpected adverse events as defined above, or any unanticipated problems involving risks to subjects, will be immediately reported to the UCSF CHR. The PI will also ensure that the OHRP are informed of any actions taken by the UCSF CHR as a result of such adverse events.

To monitor the accuracy and integrity of the data, the PI will review accumulated data approximately bi-monthly. The PI will also oversee key personnel involved in the study, maintaining contact with them on a weekly basis.

Additionally, if any subject feels that they are experiencing psychological distress, research staff will alert Dr. Joshua Woolley and the subject will be referred to counseling at his discretion, either through an appointment at the SFVAMC or UCSF or a referral to one of the community resources. The subject may also be withdrawn from the study if it is deemed to be in his or her best interest.

If a participant reports suicidal ideation, Dr. Joshua Woolley will speak with the participant and determine if the subject is a risk to him or herself and has intentions of committing suicide. The participant will be asked to contract for safety. At the doctor's discretion, a participant who reports suicidal ideation will be taken to the SFVAMC or UCSF Emergency Department for further evaluation, or if for any reason, this is not possible, SFVAMC or UCSF police will be called to handle the situation. Dr. Woolley will

use his clinical judgment to decide if a psychiatric appointment or referral to community resources is necessary.

Adequate Subject Recruitment and Enrollment
The rich resources available at the SFVAMC and UCSF and collaborations with the schizophrenia research program and clinical programs including the PART program, support the feasibility of recruiting adequate numbers of participants to successfully complete the objectives of this proposal. The study will be provided access to potential participants through collaboration with the outpatient mental health clinics at the SFVAMC and UCSF and the research recruitment team. The Schizophrenia Research Program is located at the SFVAMC and is affiliated with UCSF and the Prodromal Assessment and Research Team (PART). These programs have a great deal of experience recruiting participants and conducting research.

In our preliminary studies involving intranasal oxytocin and two visits separated by a week, we have had zero drop-outs to date. However, in our experience recruiting patients with schizophrenia in this age-group, a conservative estimate of drop out (e.g., consenting and enrolling but then using substances, not showing up, decide not to do it, etc…) is 10%. Therefore, we will attempt to recruit 89 patients over the five-year study or roughly 18 subjects per year in order to recruit the 81 patients (or roughly 16 patients per year) that we require for the proposed studies. Given that the Part program alone recruited roughly 25 new patients with recent-onset schizophrenia (of which, two thirds were male) per year over the last three years, we believe that we will be able to meet our recruitment goals.

This is a not multisite trial so the replacement of study sites is not applicable.

Minorities and Women
Minorities will be included in this study proportionally to the demographics of the Bay Area. In the current studies, we will only recruit male patients with schizophrenia. We believe this is warranted for at least two reasons. 1) Oxytocin administration may have sexually dimorphic effects. For example, intranasal oxytocin decreases amygdalar responses to fearful faces in men (Meyer-Lindenberg et al., 2011) but appears to increase amygdalar responses to identical stimuli in women (Domes et al., 2010). 2) The relationship between oxytocin responses, the menstrual cycle and sex remains unknown. For example, peripheral oxytocin levels are associated with emotion recognition abilities in both healthy and schizophrenic women but not in healthy or schizophrenic men (Rubin et al., 2010) and peripheral oxytocin levels are associated with symptom severity in women but not in men with schizophrenia (Rubin et al., 2011). Given these unknowns in the relationship between sex, the menstrual cycle, oxytocin effects and schizophrenia, we believe that beginning to investigate the effects of oxytocin only in male patients will minimize inter-subject variability and maximize the feasibility of the current studies. However, we fully acknowledge that women are underrepresented as research participants and that the same research questions apply to a female population. Thus, follow-up studies to the proposed research will include women.

Targeted/Planned Enrollment Table

Study Title: Mechanisms and Effects of Oxytocin on Social Cognition in Schizophrenia

TARGETED/PLANNED ENROLLMENT: Number of Subjects						
	Experiment 1			Experiment 2		
	Patients	Healthy Controls	Total	Patients	Healthy Controls	Total
Total Planned Enrollment	45	45	90	36	36	72
Ethnic Category						
Hispanic or Latino	10	10	20	8	8	16
Not Hispanic or Latino	35	35	70	28	28	56
Ethnic Category: Total of All Subjects *	45	45	90	36	36	72
Racial Categories						
American Indian/Alaska Native	1	1	2	1	1	2
Asian	10	10	20	8	8	16
Native Hawaiian or Other Pacific Islander	1	1	2	1	1	2
Black or African American	3	3	6	2	2	4
White	22	22	44	17	17	34
Other	8	8	16	7	7	14
Racial Categories: Total of All Subjects *	45	45	90	36	36	72

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

Department of Veterans Affairs

Memorandum

Date: September 9, 2011

From: Medical Center Director (662/00)

Subj: Career Development Award-2 Application for Joshua Woolley, MD/PhD

To: Director, Clinical Science Research and Development (121)

The enclosed Career Development Award application is submitted on behalf of Joshua Woolley, MD, PhD.

In submitting this application for funding, I assure you I am aware of the impact of the proposed research on our facility. We are extremely proud of the quality of our research program and foster a supportive environment for our investigators. The space described in the application and necessary support of the VA facility will be made available. I am pleased to submit this application with my full and enthusiastic support.

I acknowledge our commitment to submit an annual assessment and a report of Dr. Woolley's progress and development. I also acknowledge our commitment to provide 2/8 FTE during the CDA, and a 5/8 FTE from within the Mental Health Service for 1 year at the conclusion of the CDA.

Dicula Nicoll MD PhD MA

for Lawrence H. Carroll

Automated VA FORM 2105

DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420

JUL 18 2011

Director (662/00/151)
VA Medical Center
4150 Clement Street
San Francisco, CA 94121

In Reply Refer To: 10P9C

SUBJ: Fall 2011 Career Development CDA-2 LOI:
"Mechanisms and Effects of Oxytocin on Social Cognition in Schizophrenia"
Joshua Woolley, M.D., Ph.D.

1. Clinical Science R&D Service has reviewed and approved the Letter of Intent (LOI) submitted by Dr. Joshua Woolley for the Career Development program at the CDA-2 level. This LOI approval at the CDA-2 level is valid for three consecutive application review cycles, beginning with the Fall 2011 cycle. If Dr. Woolley is not approved for funding after these 3 cycles, another LOI at this level is not permitted. Applicants are reminded that awardees are not permitted to hold administrative positions.

2. Dr. Woolley is approved to submit an application with a duration of 5 years. Administrative changes to the budget and duration may occur in the review process. Any significant changes to the LOI should be approved by this office in advance of the application.

3. At this level, we are most interested in applications that show a strong relationship to diseases of concern in the VA population. The development of innovative ideas and novel questions aimed at obtaining in-depth understanding of the processes, prognoses and treatment of these diseases is encouraged. We are also interested in supporting applicants who propose a program of training that will lead to future research careers independent of the mentor(s), and reviewers will be asked to consider this overall aspect.

4. The Fall 2011 Career Development proposals will be reviewed using Grants.gov and the eRA system. It is anticipated that updated RFAs for Fall 2011 CDA-2 applications will be posted before the end of July. All proposal preparation instructions, including physician and non-physician salary requirements, must be followed.

5. Questions regarding the Career Development Program should be directed to the Career Development mailbox at vhacadereview@va.gov.

Timothy J. O'Leary, M.D., Ph.D.
Director, Clinical Science R&D Service

cc: LeRoy Frey, Ph.D.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

SOPHIA VINOGRADOV, M.D.
Professor and Interim Vice Chair of Psychiatry
Department of Psychiatry

Please Address Reply to:
Psychiatry Outpatient Service (116-C)
Veterans Administration Medical Center
4150 Clement Street
San Francisco, CA 94121
Tel: (415) 750-2073

To Whom It May Concern:

I am writing to very enthusiastically recommend to you Dr. Josh Woolley's application for the Veteran's Administration Clinical Sciences Research and Development (CSR&D) Service, Career Development Award (CDA-2). I also confirm my full commitment to serve as his primary mentor. In my experience of working with excellent medical, graduate and post-doctoral students at UCSF for the past fifteen years, he stands out as an exceptional talent in the top 1% of future researchers. He is a superb candidate for the CDA-2 award, and shows all the makings of a highly productive and successful independent investigator.

The social deficits found in schizophrenia are a devastating component of the illness and a critical determinant of patients' quality of life. However, current treatments are generally ineffective in improving these symptoms. In this application, Dr. Woolley proposes a novel and important series of studies that may lead to treatment advances for these deficits in patients with schizophrenia, and possibly other psychiatric illnesses as well. Dr. Woolley will investigate the effects of intranasally administered oxytocin on social cognition and behavior, and on neural and peripheral responses to social stimuli, in patients with schizophrenia. Oxytocin could prove to be an effective method for increasing patients' social functioning, making psychotherapeutic interventions for schizophrenia more effective, and improving patients' quality of life. Such findings would change our model of care for veterans with schizophrenia and other serious mental illnesses, including PTSD, TBI, and substance abuse. The implications for the clinical care of veterans and for public health would be large.

Dr. Woolley's Background and Qualifications

Dr. Woolley is currently a post-doctoral research fellow in my research group at the Schizophrenia Research Program at the San Francisco Veterans Affairs Medical Center and University of California, San Francisco (UCSF). . Dr. Woolley and I first met seven years ago, when he worked in my clinic as a third year medical student. The genuine scientific curiosity and clinical enthusiasm that were immediately evident at this meeting so long ago have only grown over the ensuing years. I have been continually and increasingly impressed by his intelligence, self-motivation, drive, and focus. When he started working in my psychopharmacology clinic as a medical student, Dr. Woolley already demonstrated an unusually high level of clinical poise, thoughtfulness, and compassion. When he returned to work in the clinic again as a resident several years later, I was very pleased by his continuing growth in the personal, clinical, and scientific domains. It has been my great joy to support him in his development as an exemplary clinician and outstanding scientist.

Dr. Woolley has achieved a remarkable series of research accomplishments during his time at UCSF. While in the Medical Scientist MD/PhD Training Program, he forged a unique collaboration between a basic neuroscientist, Howard Fields, and a clinical researcher, Bruce Miller. His graduate work involved animal and human research, leading him to develop both basic and clinical research skills. Moreover, Dr. Woolley was extraordinarily

productive as an MD/PhD student. He has published influential first-authored papers in *Neuroscience* and *Neurology*. During his clinical training, he also published several interesting case in *American Journal of Psychiatry*, *Neurology,* and *General Hospital Psychiatry*. Dr. Woolley is exceptionally productive and he has already made important contributions to the medical and neuroscientific literatures.

After completing the M.D./Ph.D. program, Dr. Woolley focused on clinical training in psychiatry, and increasingly became interested in the functional problems caused by prominent social cognitive deficits in patients with schizophrenia, Two years ago, he came to me with an interest in investigating whether oxytocin's known prosocial effects could be harnessed to ameliorate the social cognitive deficits of schizophrenia. His timing was perfect given my increasing focus on social cognition in schizophrenia and the recent award of a 5-year NIMH RO1 grant to perform a trial of neuroscience-guided social cognitive training in schizophrenia. Dr. Woolley has since designed and begun to carry out a series of elegant experiments to investigate the effects of oxytocin in schizophrenia as both a predictor and possibly as an adjunct to treatment. Additionally, he designed a study looking at the effects of exogenous oxytocin on social behavior of family members of patients with schizophrenia. Over the past year and a half, despite having significant clinical duties, he has been highly productive, designing the experiments, obtaining IRB and FDA approval and developing collaborations with experts in oxytocin biology. He has also obtained independent intramural funding for two of his studies and has developed productive mentoring relationships with key faculty members at the SFVAMC and UCSF. Josh's studies are truly innovative and will have a high impact on the field.

Dr. Woolley is also a gifted educator and a budding mentor himself. He consistently shows a genuine interest in helping more junior colleagues. I have been amazed by his ability to recruit undergraduate students as volunteer researchers and to harness their energy and enthusiasm. He is a natural leader and his ability to create his own "volunteer army" with a common vision and purpose has been extremely impressive. He also started and continues to lead our biweekly journal club where junior researchers learn how to critically read, evaluate, and present scientific articles. Given his significant mentoring and leadership skills and genuine warmth and concern, he is already an outstanding mentor to trainees of all stripes and I am confident he will be an excellent asset to the SFVAMC's training mission.

In addition to his strong research and teaching skills, Dr. Woolley is completely committed to building a successful career in the VA Healthcare System as s a physician scientist who specializes in the biology of mental illnesses. Our supervision sessions have often focused on professional development and on the roadmap to becoming a successful principal investigator at the VA. While investigating the effects of oxytocin in patients with schizophrenia is an excellent place to start developing his program of research, Dr. Woolley's ideas have broader applications, including to patients with substance abuse and histories of trauma. I am confident that as Dr. Woolley continues to develop and grow his program of research at the SFVAMC, he will become a critical component of our veteran-focused research endeavors.

Dr. Woolley has demonstrated the ability, creativity, and commitment to achieve his goals and I commit to work with him to help him realize his full potential. I have greatly enjoyed working with him and am committed to helping him progress. I am confident that Dr. Woolley will be a major asset to the VA health system. He also has the potential to advance our understanding and treatment of schizophrenia. In light of Dr. Woolley's future

goals, this CDA-2 award will be critical to his growth and development to become an independent clinical scientist at the VA.

To summarize, Dr. Woolley is a superbly trained young investigator and a highly creative, innovative, energetic, and productive investigator. He is an enthusiastic, dedicated, and ethical researcher who never forgets the human side of the disease even as he applies the most rigorous methodology to his investigations. Dr. Woolley is poised to make highly significant and original contributions to a translational clinical approach to social cognitive deficits in psychotic illness and neuropsychiatric illness more generally. He has already demonstrated his dedication and commitment to translational neuroscience and to the VA medical system, and has made important contributions to the study of the neurobiology of reward. Overall, he has proved to be a highly productive and creative independent investigator who is certain to make innovative and high-impact findings in the realm of human behavior.

Research Environment and Primary Mentor Support

During his CDA-2 award period, Dr. Woolley will be a member of a resource-rich, world-class biomedical research environment. . UCSF is among the top 5 medical science research universities in the U.S., while the SFVAMC has the highest rate of extramural research funding of any VA medical center. My research program in schizophrenia at the SFVAMC will provide him access to well-characterized cohorts of patients with schizophrenia. My current funding includes three R01's on which I am the principal investigator that support research into the behavioral and neural marker effects of specific forms of neuroscience guided, computerized cognitive training in adults with schizophrenia, adolescents with recent-onset psychosis, and persistently mentally ill adults in a real-word, supported employment community setting. Additionally, one of the R01 grants focuses on the effects of training module that addresses social cognition. Dr. Woolley's developing program of research is a perfect complement to this research and his work will both synergize with and complement our ongoing studies. His office is in immediate proximity to my laboratory and to the lab of Dr. Daniel Mathalon, Dr. Woolley's co-mentor and an expert in neuroimaging in schizophrenia. Dr. Woolley will have access to computers, statistical software, a dedicated psychophysiology laboratory, and all necessary equipment to conduct the experiments described in his Career Development Award. Through our affiliation with UCSF, he will be able to take advanced coursework in neuroimaging theory and practice, psychophysiology, and advanced statistical analysis.

I spend 50% of my time in the conduct of research and am presently mentoring 1 M.D. resident research fellow, 2 Ph.D. postdoctoral fellows, and 2 junior faculty members with career development awards. A number of my prior fellows hold academic appointments at leading academic institutions. A partial list is attached to this letter. As Dr. Woolley's primary mentor, I will meet with him at least weekly, and we will have a larger group meeting with his other mentors twice per year. I will advise him on his research study and on career development. Our mentorship meetings will focus on the design, implementation, analysis, and dissemination of experimental studies with clinical populations suffering from severe psychiatric illness. In addition, we have weekly group research meetings where we discuss data analysis, research methodology, manuscript preparation, and grant writing. I will challenge him to think about his data in the context of conceptual models and theory. I will help him gain a more sophisticated understanding of the neurobiology of schizophrenia by guiding his reading of the literature and discussing the field with him at a theoretical and conceptual level. I expect that Dr. Woolley will publish at least three first-authored papers

per year from the proposed work during the award period, and we will emphasize the publication of high-impact findings. Finally, during the last two years of the award period, I will work with Dr. Woolley to help him transition into an independently funded academic position. This will include helping him apply for VA Merit and NIMH R01 funding, entering the academic job market, and negotiating for space and resources.

In sum, I support Dr. Woolley enthusiastically and without reservation for this CDA-2 award. He is creative, collaborative, dedicated, scientifically astute, an excellent critical thinker, and he is completely committed to a career as an independent investigator conducting VA mission-relevant research. He is one of the most motivated and dedicated young investigators I have ever worked with, and has the real "fire in the belly" that is necessary for a successful scientific career. I feel privileged to have been a part of his development as a scientist and clinician thus far, and I know that he will make high impact contributions to the scientific community. I will continue to support Dr. Woolley's work and I will do all that I can to promote his professional development.

Please do not hesitate to contact me if any further information is needed.

Sincerely,

S. Vinogradov MD

Sophia Vinogradov, M.D.
Professor and Interim Vice Chair of Psychiatry
University of California, San Francisco

Research Postdoctoral Fellows

Name	Years Trained	Current Employer	Current Title
John H. Poole, Ph.D.	1993-1996	Palo Alto VAMC/ Stanford	Dir. of Research, TBI Unit; Adjunct Associate Professor
Michael Minzenberg, M.D.	1997-2003	UC Davis	Assistant Professor
Stewart Anderson, M.D.	1999-2001	Cornell University	Assistant Professor
R. Alison Adcock, M.D., Ph.D.	2001-2006	Duke University	Assistant Professor
Rachel Loewy, Ph.D.	2005-2006	UC San Francisco	Adjunct Assistant Professor
Karuna Subramaniam, Ph.D.	2007-present	UC San Francisco	Post-doctoral fellow

UCSF
University of California
San Francisco

San Francisco VA Medical Center

Daniel H. Mathalon, Ph.D., M.D.
Professor in Residence of Psychiatry
Co-Director, Brain Imaging and EEG Lab

Mental Health Service 116D
4150 Clement St.
San Francisco, CA 94121
Phone: (415) 221-4810, ext.3860
E-mail: daniel.mathalon@ucsf.edu

August 30, 2011

To Whom It May Concern,

I am writing this letter to enthusiastically support the application of Dr. Joshua Woolley for a VA Research Career Development Award. I have known Josh for the last three years, and I have had the opportunity to observe him in both research and clinical settings. I have been continually impressed by his genuine curiosity and enthusiasm as well as his obvious intellect and his ability to successfully and independently complete difficult research projects. During the time that I have known him, Josh has developed and implemented a novel program of research focusing on the neurohormonal underpinnings of social deficits in patients with schizophrenia. This work is elegantly designed and addresses an important research question. Josh has synthesized a large, complicated literature, has recognized an important unanswered question and has assembled a strong mentoring team to help him successfully complete his proposed studies. This work has a high chance of contributing important new insights to our understanding of social cognition impairments in schizophrenia, and I am confident that Josh will be able to successfully complete the proposed research.

Josh has an impressive track record. He has been highly productive and has repeatedly demonstrated a striking creativity in investigating the neural substrates of human behavior. His ability to define important research questions and leverage scientific resources to find answers is very impressive. Also of note, his recruitment and mentorship of research assistants and trainees are demonstrated strengths. All of these qualities contribute to why I believe that Josh will be a leader in academic research. I feel privileged to have been a part of his development as a scientist and clinician, and I'm confident that he will be a true asset to the scientific community and the VA

Clinically, Josh has a kind and confident bedside manner that patients find comforting. In addition to his deep knowledge of pharmacology and psychiatric illness, he demonstrates an impressive ability to astutely formulate difficult cases and then to implement effective treatment plans for these patients. He is also a joy to work with. Josh will be an asset to any clinical service that he joins within the VA system.

Josh has assembled an outstanding mentoring team to help him successfully complete the proposed projects and to develop to his full potential as an independent social neurobiologist. I already have an excellent collaborative relationship with Dr. Vinogradov and while I already know Drs. Mendes and Rankin, I look forward to working more closely with them as we co-mentor Josh. With regard to my own mentoring responsibility, Josh requires further training in functional neuroimaging techniques such as event-related and functional connectivity analyses. Given my extensive experience and training in using these techniques, I am confident that I can successfully mentor Josh in obtaining these skills. I will meet biweekly with him. During these meetings we will discuss topics including design of fMRI experiments (e.g., event-related and block study designs), stimuli selection and coding, data collection, image pre-processing, data analysis techniques and manuscript preparation. I will also supervise Josh's overall

progress on learning these skills and will check in with him concerning his neuroimaging related courses and seminars and will ensure that he is getting optimal benefit from his training activities. We will also discuss issues regarding professional development. In addition to my time, I will provide Josh with adequate computer resources, including hardware and software, for him to successfully analyze and interpret the data from his proposed studies. Towards the end of the award period, I will assist Josh with applying for independent funding such as a VA merit award and an NIH R01. I am confident that Josh will publish numerous high-impact articles from the data he collects from his proposed studies.

I spend 50% of my time in the conduct of research, 25% of my time teaching, and 25% of my time in clinical and administrative duties. I am currently mentoring 2 M.D. research-track residents, 2 Ph.D. postdoctoral fellows, and 1 junior faculty member with a career development award. I have also mentored numerous psychiatry residents (including Dr. Woolley) and psychology fellows in the past decade, with many of my mentees successfully competing for NARSAD grants and securing faculty positions in psychology or psychiatry departments around the country. A partial list is attached to this letter. Due to my training in psychology and psychiatry, I feel that I am an ideal mentor for Josh and well suited to guiding his program of research.

In my experience of working with many excellent medical and graduate students over the past fifteen years, Dr. Woolley stands out as an exceptional talent. He has already made important contributions in the field of neuroscience and I am sure that he will make major scientific contributions in the future. As such, I am happy to recommend him in the strongest possible terms. Furthermore, I am honored and excited to be asked to mentor Josh in his proposed endeavors and will do my best to help him achieve his research and career goals. Josh is an ideal candidate for this award.

Please do not hesitate to contact me if you have any questions about Dr. Woolley's application. Again, I could not be more enthusiastic about offering my support to him, and I believe the VA's Career Development Award is an ideal fit with his current research and career development goals.

Sincerely yours,

Daniel Mathalon, PhD, MD

University of California

UCSF

San Francisco
Department of Psychiatry
School of Medicine

Wendy Berry Mendes, PhD
Sarlo/Ekman Professor of Emotion
UC San Francisco
401 Parnassus Ave
San Francisco, CA 94143-0848
Tel: (415) 476-7409
Fax: (415) 476-7744
Email: Wendy.Mendes@ucsf.edu

September 5, 2011

Dear grant review committee members:

I am delighted to be writing a letter of support for Dr. Joshua (Josh) Woolley who is applying for a Career Development Award. I have known Josh for just over a year since I began my appointment at UC San Francisco in the fall of 2010. In that time I have worked closely with Josh while he designed and implemented four studies in my lab, submitted several small and large grants, and led a popular tutorial for summer interns in my lab. Even though a year is not a particularly long time as a supervisor, because of the scope of his projects and the intensity with which Josh works, I am in an excellent position to comments on his qualifications and career trajectory.

As mentioned Josh has several on-going collaborations with me in the Emotion, Health and Psychophysiology lab that I direct. Indeed, Josh was one of the first people at UCSF to contact me regarding collaborating once I accepted the UCSF offer. At that first meeting after about ten minutes of talking to Josh, I knew he would be a great fit for my lab and a fun young scholar to supervise. Although I am often reluctant to take on mentees in my lab without a long trial period in which they work closely with established lab members on joint projects, I did not have Josh go this route. Instead, I allow Josh to develop his independent projects from the beginning.

I won't mention all the different studies that Josh is spearheading in my lab, but I will mention one that serves as preliminary data for the study he is proposing in this grant. Josh's approach to buffering the potentially devastating path of schizophrenia is informed by both biological and psychological sciences. In several studies now Josh has been examining the acute effects of oxytocin on social and emotional functioning. What is particularly novel with Josh's work is that he is applying this biological model to a young sample with recently diagnosed schizophrenia and looking at the behavioral and neurophysiological effects of this intervention. Though the effects of oxytocin in increasing trust and social accuracy among non-mentally ill individuals is clear, it is an open question whether the effects of oxytocin will show the same benefits with individuals with mental illness (though there is new emerging data to strongly suggest that it will). Josh's approach is truly translational, bridging basic and clinical approaches utilizing techniques from multiple disciplines. This work is elegant and will lead to high-impact findings.

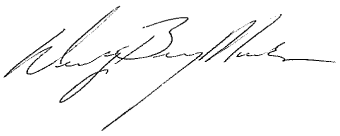
In addition to his research endeavors, Josh is a committed teacher and mentor. He supervises his own "team" of research assistants and, when watching him interact with them, I am struck by the

natural leadership qualities Josh possesses. He is not only brimming with ideas and excited about science, but he is also generous with his time and attention. Josh explains the rationale behind the studies and is patient with the research assistants, yet is never condescending and makes his team feel like they hold equal partnerships in the science conducted. He also led a tutorial for the 20 summer interns I had in my lab this summer, and the interns rated his tutorial the best of all the post-docs. I wasn't surprised by this; Josh's enthusiasm is inspiring and contagious. I have read and discussed the grant with Josh and am as excited about the science as he is.

Without question my best mentees have been individuals who are not only smart and dedicated but also who explore questions that I find exciting to explore (I have included below a table of my past mentees and their subsequent positions). If funded, I would work closely with Josh on his behavioral studies particularly with the social, emotional, and physiological outcome variables, for which I have expertise. Additionally, I will assist Josh with the statistical analyses that will be required with his data set –most specifically data analyses to examine the effects of oxytocin on physiological responses to emotional stimuli and how these responses might underlie other pro-social effects oxytocin. These analyses will require a series of hierarchical linear modeling/mixed modeling approaches, for which I have extensive expertise. Josh has a good intuitive sense of statistics, and I feel confident that he will be able to master these analytic approaches with some supervision and instruction.

In many ways Josh represents the future of science. He approaches research questions from multiple levels of analysis, is well-trained clinically and methodologically, has a sophisticated theoretical approach yet is translational in the application of what he learns, and is a natural and gifted teacher and mentor. He is clearly someone worthy of substantial investment. Indeed, if I could buy stock in Josh, I would buy all of it. He is a "sure-bet" for several reasons. First, his track record for publishing is excellent from both a quality and quantity perspective. Second, his research questions are likely to bring about answers to important questions and receive attention from researchers within and across his primary fields. Finally, he has tremendous potential as a clinician, teacher and mentor. Josh is bright, thoughtful, thorough, creative, and socially adept. He is poised to be a leader in the academic and research fields.

Best regards,



Wendy Berry Mendes, Ph.D.

PREDOCTORAL STUDENTS SUPERVISED OR MENTORED

Dates	Name	Department	Role	Current Position
2004-2009	Modupe Akinola	Organizational Behavior	PhD advisor	Asst Professor Columbia University
2004-2010	Karim Kassam	Social Psychology	PhD co-advisor	Asst Professor Carnegie Mellon
2004-2008	Kristina Olson	Social Psychology	Supervised research	Asst Professor Yale University
2005-2010	Katrina Koslov	Social Psychology	PhD advisor	Research Scientist UCSF
2006-pres	Matt Killingsworth	Social Psychology	Supervised research	Harvard graduate student
2007-pres	Amitai Shenhav	Cognitive Psychology	PhD advisor	Harvard graduate student

POST-DOCTORAL STUDENTS SUPERVISED OR MENTORED

Dates	Name	Fellow	Role	Current Position
2005-2007	Carlos Navarette	Psychology	Supervised research	Asst Professor Michigan State
2006-2009	Kristin Shutts	MBB post-doc scholar	Supervisor	Asst Professor University Wisconsin
2008-2009	Elizabeth Page-Gould	Social Psychology	Supervisor	Asst Professor Toronto University
2008-2010	Elizabeth Sweet	HSPH RWJ-scholar	Supervisor	RWJ scholar
2008-2010	Fiery Cushman	MBB scholar	Supervised research	Asst Professor Brown University
2009-2010	Chris Oveis	Psychology	Supervisor	Asst Professor UC San Diego
2009-pres	Jeremy Jamieson	Psychology	Supervisor	NRSA post-doc

University of California
San Francisco

UCSF

Department of Neurology
Memory and Aging Center

Alzheimer's Disease Research Center (NIH)

California Alzheimer's Disease Center (DHS)

350 Parnassus Avenue, Suite 905
San Francisco, CA 94117
tel: 415/476-6880
fax: 415/476-4800
memory.ucsf.edu

Mailing Address:
UCSF Box 1207
San Francisco, CA 94143-1207

September 1, 2011

Dear Selection Committee Representatives,

I enthusiastically support Dr. Joshua Woolley's application for a VA Career Development Award. Dr. Woolley has proposed a groundbreaking, valuable, yet practically feasible series of studies, and his preliminary work in this area is already showing promising results. With the help of this award, he will be in a position to make important contributions to our understanding of the neurobiology of social cognition and behavior as well as to develop treatments for deficits in these domains.

I am a principal investigator at the Memory and Aging Center at UCSF, and I specialize in the anatomic basis of social cognitive and behavioral deficits in neurodegenerative disease. I have worked with Dr. Woolley for many years, beginning when he sought out Dr. Bruce Miller at the Memory and Aging Center to be his scientific mentor during his M.D./Ph.D. program. During this time, it has become clear to me that Dr. Woolley is a naturally gifted researcher, consistently impressing me with his intelligence, drive, and creativity. Even at a very early stage of his medical education, Josh demonstrated rare talent and keen curiosity in his scientific pursuits, which has led him to habitually synthesize knowledge and techniques from multiple disciplines in tackling complex research questions. Soon after Josh joined the Memory and Aging Center, he envisioned, designed, and implemented a complex and entirely novel study of feeding and hormonal abnormalities in patients with various forms of neurodegenerative disease. This work has led to several influential publications.

For the first years of our collaborative working relationship, I supported Dr. Woolley's research by helping him coordinate his data collection with other projects within the Memory and Aging Center. Over the last year, I have taken on a more direct mentorship role and provide both intellectual and institutional support for his investigations. We now meet together on a weekly basis to discuss research design and procedure, perform statistical analyses, and plan the dissemination of his results. I will continue to mentor and support Dr. Woolley as he carries out the studies in this proposal, and will work with him to ensure rigorous analysis and timely publication of the data. In particular, I will continue to meet with Dr. Woolley on a weekly basis and will mentor him as he develops expertise in advanced statistical techniques including multipredictor and longitudinal modeling, and will also provide guidance around selection and interpretation of tests of social cognition. I will also meet with Dr. Woolley and his other mentors at least twice per year. Finally, I will guide Dr. Woolley in manuscript and grant preparation and will work collaboratively with his other mentors in advising his career and professional development. I am confident that I will be able to successfully mentor Dr. Woolley as I have substantial experience training and supervising junior researchers (see table below).

The capacity to define important research questions, then adroitly leverage scientific resources to find answers, are abilities that will enable Josh to be a leader in academic research. Given Dr. Woolley's impressive personal qualities, his outstanding project, his world class mentoring team and the rich resources available to him, I am confident that he will successfully complete the proposed studies and will become a leader in the field of social neurobiology. I am honored to be a part of his development as a scientist and clinician, and will help him successfully complete these exciting studies.

Sincerely,

Katherine P. Rankin, PhD
Associate Professor
UCSF Department of Neurology
krankin@memory.ucsf.edu

POSTDOCTORAL FELLOWS MENTORED

Dates	*Fellow Name* *Program*	*Project*
2007 - 2010	**Marc Sollberger, M.D.** Visiting Neurologist (Switzerland)	Structural Anatomy of Personality in Neurodegenerative Disease
2007 – current	**Joshua Woolley, M.D., Ph.D.** UCSF Psychiatry Resident	Frontotemporal Dementia Feeding Study
2008 - current	**Winston Chiong, M.D., Ph.D.** UCSF Neurology Flexible Residency Program	Moral Reasoning in Frontotemporal Dementia
2009 – 2010	**Virginia Sturm, Ph.D.** UCSF Neuropsychology Fellow	Self versus Other Awareness in Neurodegenerative Disease
2009 – 2011	**Carmela Tartaglia, M.D.** UCSF Neurology Fellow	Genetic Contributions to Social and Emotional Behavior
2009 – current	**Tal Shany-Ur, Ph.D.** UCSF Research Fellow	Theory of Mind in Neurodegenerative Disease
2010 – current	**Amanda Lamarre, Ph.D.** UCSF Neuropsychology Fellow	Longitudinal Analysis of Personality Change in Dementia
2011 – current	**Jennifer Yokoyama, Ph.D.** UCSF Genetics Fellow	Normal Structural Neuroanatomic Correlates of BDNF haplotype
2011 – current	**Suzee Lee, M.D.** UCSF Neurology Fellow	Clinico-pathologic characterizations of bvFTD

FACULTY MENTORING

Dates	*Faculty Name* *Position While Mentored*	*Mentoring Role*	*Current Position*
2002—2003	**Allyson Washburn, Ph.D.** Assistant Professor of Psychology	Research Advisor for NIH grant application	Assistant Professor Saybrook Graduate School
2002—current	**Heidi Kirsch, M.D.** Assistant Professor In Residence	Research Collaborator/Advisor for her K-series NIH award	Assistant Clinical Professor UCSF Dept. of Neurology

PREDOCTORAL STUDENTS MENTORED

Dates	*Student Name* *Program or School*	*Mentoring Role*	*Current Position*
2004	**Emily Baldwin** UCSF Medical Student III	Research Elective Supervisor	Psychiatry Residency UCSF
2004 – 2006	**Sara Howard** Alliant University	Doctoral Thesis Research Advisor	Psychology Graduate Student
2005	**Wendy Santos-Modesitt** UCSF Summer Research Training Program	Research Supervisor	Psychology Graduate Student Alliant University
2005 – 2006	San Francisco State University	Senior Thesis Research Supervisor	
2007 – 2008	Alliant University	Master's Thesis Research Supervisor	
2005 – 2006	**Anli Liu** UCSF Medical Student III	MD with Thesis Supervisor	Neurology Residency Cornell
2004-2007	**Joshua Woolley** UCSF Medical Student	Research Supervisor	Research Fellow UCSF
2006	**Andrea Salazar** UCSF Summer Research Training Program	Research Supervisor	Psychology Graduate Student Fresno State Univ.
2007	**Mary Catherine Mayo** USC Medical Student III	Research Elective Supervisor	Medical Student Univ. Southern California
2008	**Evi Lykou** Athens General Hospital	Research Supervisor	Psychology Graduate Student Athens, Greece
2008-2009	**Alefiyah Pishori** MAC Research Coordinator	Research Supervisor	Psychology Graduate Student University of Connecticut
2008 – 2011	**Eric Strobl** UC Berkeley Undergraduate	Research Supervisor	Undergraduate Student UC Berkeley
2008 – 2011	**Nikhil Murthy** UC Berkeley Undergraduate	Research Supervisor	Undergraduate Student UC Berkeley
2009 – present	**Baber Khan** UC Berkeley Undergraduate	Research Supervisor	Research Coordinator UCSF Dept. Neurology
2009 – 2011	**Jessica Bol** Alliant University	Research Supervisor	Psychology Graduate Student Alliant University
2009 – 2010	**Parnian Toofanian** Practicum Student	Research Supervisor	Psychology Graduate Student Stanford University
2010	**Lisa Veldheusen** Medical Student	Research Supervisor	Erasmus Medical School Netherlands
2010	**Cordula Felix** Medical Student	Research Elective Supervisor	Erasmus Medical School Netherlands
2011	**Nancy Lin** Medical Student	Research Elective Supervisor	University of Texas Medical School
2011	**Gianina Toller** Neuropsychology Grad Student	Research Supervisor	Univ. Hospital Basel Switzerland
2010-2011	**Eduardo Galeana** UCSF Summer Research Training Program	Research Supervisor	Psychology Graduate Student San Francisco State Univ.

U N I V E R S I T Y O F I L L I N O I S
A T C H I C A G O

The Brain-Body Center
Department of Psychiatry
The Psychiatric Institute (MC 912)
1601 West Taylor Street
(312) 355-1593 (phone)
(312) 996-7658 (fax)

C. Sue Carter, Ph.D
Professor of Psychiatry
Co-Director, BBC
Chicago, Illinois 60612

August 7, 2011

Dr. Josh Woolley
Department of Psychiatry
University of California, San Francisco
San Francisco, CA

Dear Josh,

This letter is to confirm my enthusiastic support for your proposed research on the effects of oxytocin in schizophrenia. The proposed experiments are strongly justified by your own preliminary data, as well as recent preclinical and clinical evidence showing that in schizophrenia oxytocin reduces psychotic symptoms and improves social cognition. Your studies are innovative in examining mechanisms through which exogenous oxytocin may improve emotional and cognitive function in this disorder. As you are proposing, it is also critical to add knowledge of endogenous peptides, including oxytocin and vasopressin, to the analysis of the effects of manipulations of exogenous oxytocin.

We have measured oxytocin in human samples from individuals with psychiatric and neurological disorders including schizophrenia, autism, postpartum depression and Williams Syndrome. Results from these studies reveal significant relationships among peripheral endogenous levels of oxytocin and various behavioral outcomes. For example, one of these studies revealed that plasma oxytocin levels were low in patients diagnosed with a particularly intense form of schizophrenia with water imbalance (Goldman, et al., 2008). More recently, in collaboration with the laboratory of Dr. Janice Kiecolt-Glaser, we found significant correlations between endogenous blood levels of oxytocin and both positive social interactions and wound healing (Gouin, et al., 2010). We also have completed a systematic analysis of blood levels of oxytocin in schizophrenic patients (Rubin, et al., 2010 and 2011*)*; these studies revealed that higher endogenous levels of oxytocin were associated with fewer positive symptoms and social deficits, especially in women. Knowledge from these studies will be used to advise you in the design, measurement and interpretation of oxytocin data in your projects.

It has been my good fortune over a long career to mentor dozens of excellent basic scientists, including several students doing clinical studies. I will be pleased to use this experience to help you in your own career development. Your excitement and commitment to research are infectious. Obviously you have excellent training in neuroscience and medicine, and it is critical that you continue to extend and apply these skills in the context of the proposed research. The potential public health impact of this study is tremendous and I am very optimistic for your success, and the success of the proposed studies.

Warmest regards,

C Sue Carter

C. Sue Carter, Ph.D

Penn Medicine
University of Pennsylvania School of Medicine

Division of Neuropsychiatry
David I. Leitman, PhD
Research Assistant Professor, Brain Behavior Laboratory
Department of Psychiatry

5 September 2011

To: Scientific Review Committee

Re: **Career Development Award proposal of Joshua Woolley MD/PhD**

Dear Committee members,

It is with great pleasure that I write to support Joshua Woolleys' CDA application "The effects of intranasal oxytocin on social deficits in recent-onset schizophrenia". I have been collaborating with Dr. Woolley for over a year now. His investigations into the effects of oxytocin on social communication in schizophrenia dovetails nicely with my own interests in affective prosody.

As you may well know, negative symptoms such as blunted facial affect and lack of prosody have been increasingly shown to portend poor functional outcome for patients. There is a concerted effort afoot to understand the nature of these deficits as well as identify effective treatments. Therefore, Dr. Woolley's proposal to study oxytocin as a possible adjunctive therapy for negative symptoms is of great import.

For my part, I pledge to continue to aid Dr Woolley's ongoing investigation by consulting with him regarding his experiments measuring vocal affect communication in patients with schizophrenia.

Additionally, through his collaboration with me here at Penn, Dr. Woolley will be able to benefit from current multi-disciplinary approaches under way within our department and the department of Bioengineering here at Penn to develop automated computer algorithms for classifying vocal and facial affective communication in healthy individuals and patients with schizophrenia. These 'machine learning' approaches are cutting edge and still developing, but they will augment conventional acoustic feature analysis and facial affect analysis using FACES, provide an objective measure of emotionality for facial and vocal gestures, that are not tethered to human raters.

I look forward to collaborating with Dr. Wooley on this exciting project.

Sincerely,

David Leitman, Ph.D.

10th Floor Gates Pavilion | 3400 Spruce Street | Philadelphia, PA 19104 | 215-662-7389 | Fax: 215-662-7903 | leitman@upenn.edu

UNIVERSITY OF ILLINOIS
AT CHICAGO

The Brain-Body Center
Department of Psychiatry
The Psychiatric Institute (MC 912)
1601 West Taylor Street
Chicago, Illinois 60612

Stephen W. Porges, Ph.D.
Professor of Psychiatry
Director
E-mail sporges@psych.uic.edu
(312) 355-1557

August 23, 2011

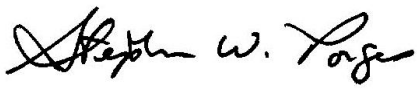
Re: letter of support Dr. Joshua Woolley

I enthusiastically support Dr. Woolley's proposed research and am pleased to serve as a consultant on his project. His project is novel, feasible, and will potentially have high impact. Dr. Woolley's project will provide insights into the effects of oxytocin on social cognition and behavior in patients with schizophrenia and will provide additional fundamental information to further our understanding of the underlying neurophysiological mechanisms through which oxytocin enhances of social behavior. In particular, his proposed simultaneous measurement of social behavior, peripheral and central neurophysiological responses, and eye-gaze patterns will provide an opportunity to understand the interactions and integration of these response systems and will lead to substantial advancements. I will be pleased to share my expertise in the neuroanatomical and psychophysiological substrates of social behavior to help Dr. Woolley successfully complete the proposed studies.

My laboratory focuses on a phylogenetic model of the autonomic nervous system called the Polyvagal Theory (Porges, 1995). The theory provides a reconceptualization of the autonomic nervous system leading to a new understanding of how the autonomic nervous system selectively reacts to specific challenges and is regulated by brainstem structures that are also involved in the regulation of neuropeptides (e.g., vasopresssin and oxytocin). The theory incorporates an understanding of the phylogenetic shifts in the neurophysiological mechanisms that mediate autonomic reactivity. This theory challenges researchers to conceptualize autonomic regulation as an important substrate mediating several psychological and behavioral features associated with typical and atypical development. Dr. Woolley's research is based on this theoretical framework and his studies test several key hypotheses that stem from the Polyvagal Theory. I have extensive experience developing and applying new technologies in psychophysiology that are applicable to developmental and clinical populations. I will be pleased to share my knowledge and expertise to assist Dr. Woolley in the design, measurement, and interpretation of data from his projects.

I have successfully mentored numerous basic and clinical scientists who have gone on to academic appointments. I am confident that I will be able to do the same for Dr. Woolley, who has impressed me with his creativity, enthusiasm, and intelligence. I look forward to supporting Dr. Woolley's research agenda and in helping him develop into an independent clinical researcher. His scientific agenda will be accelerated by this award and the knowledge generated by the proposed studies will have significant impact on society and public health.

Sincerely,



Stephen W. Porges, Ph.D.
Professor of Psychiatry and Bioengineering

UIC
Phone (312) 413-3295 • Fax (312) 996-7658 • Email bbc@psych.uic.edu

Department of Veterans Affairs

Memorandum

Date: September 1, 2011

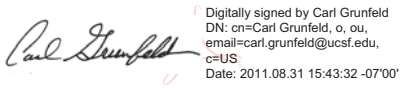
From: ACOS for Research and Development (151)

Subj: Career Development Award-2 Application for Joshua Woolley, M.D., Ph.D.

To: Director, Clinical Science Research and Development (121)

1. The enclosed Career Development Award-2 application is submitted on behalf of Joshua Woolley, M.D., Ph.D.

2. I write to express my enthusiastic support for the application of Dr. Woolley for a Career Development Award-2. I acknowledge my commitment to submit an annual assessment of Dr. Woolley's progress and development.



Carl Grunfeld, M.D., Ph.D.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO

SANTA BARBARA • SANTA CRUZ

SOPHIA VINOGRADOV, M.D.
Professor and Interim Vice Chair of Psychiatry
Department of Psychiatry

Please Address Reply to:
Psychiatry Outpatient Service (116-C)
Veterans Administration Medical Center
4150 Clement Street
San Francisco, CA 94121
Tel: (415) 750-2073

To Whom It May Concern,

If Dr. Joshua Woolley is awarded the Career Development Award, his clinical duties will include attending in outpatient clinics at the San Francisco VA Mental Health Service for no more than 25% of his time.

Sincerely,

S. Vinogradov MD

Sophia Vinogradov, M.D.
Professor and Interim Vice Chair of Psychiatry
University of California, San Francisco

July 19, 2011

RE: Joshua Woolley application for a Veterans Administration Career Development Award

I am writing to support the application of Joshua Woolley for a Veterans Administration Career Development Award. I was Dr. Woolley's PhD supervisor for his graduate studies in neuroscience while he was in the Medical Scientist Training Program at UCSF.

In my laboratory, Dr. Woolley's work addressed the problem of sensory specific satiety. He designed and carried out a series of highly informative experiments demonstrating that opioid actions in the ventral striatum can promote feeding that is selective for palatable food items. In addition, and unexpectedly, when rodents are given a choice between two palatable items, Josh found that opioids in the ventral striatum selectively promote consumption of the food having the preferred taste. This effect was apparently due to reversal of sensory specific satiety. Josh's work was careful, the data was analyzed rigorously and it was clear that he read the relevant literature with interest and with care. I found his thinking to be very sophisticated.

While Josh certainly excelled in his graduate research with me, another truly exceptional aspect of his accomplishment is that he simultaneously carried out a related clinical research project with Bruce Miller, director of the UCSF memory and aging center. In those studies he investigated patients with fronto-temporal dementia and made a new, possibly seminal discovery. He discovered a sub-group of patients who had markedly increased food consumption, i.e. a failure of normal satiety mechanisms. Using voxel based morphometry to analyze anatomical data derived from magnetic resonance imaging, he showed that these patients had a highly selective degeneration in a region of the right insular cortex. What is exceptional about these studies is that they were carried out in the General Clinical Research Center and required assembling a team of individuals to design and deliver the food and to keep track of patients' consumption. It also required analyzing the data and correlating it with changes in particular brain regions. This project speaks to Dr. Woolley's drive, focus and organizational skills.

I believe that Dr. Woolley is a superior candidate. He has shown exceptional skills in a number of areas related to both animal research and patient care. He has exhibited both deep curiosity about behavioral phenomena and compassion for the clinical problems that afflict patients with behavioral abnormalities. I believe that he is ideally suited to carry out the project on the effects of oxytocin in schizophrenia. This is a novel idea with great promise. In addition, he has demonstrated excellent work habits, research focus, and interpersonal skills. He is highly motivated in the areas of patient care and research and is a natural scholar. In his medical/graduate school career he has been highly productive in terms of publications. At a personal level, he exhibits calm and a mature demeanor that I am sure will put patients (and colleagues) at ease. He has demonstrated his ability

to do independent research and he has excellent potential for an academic career. I recommend him with great enthusiasm.

Sincerely yours,

Howard L. Fields MD PhD

Professor of Neurology, Physiology and Psychiatry In-residence
Director, Wheeler Center for the Neurobiology of Addiction
Investigator, Ernest Gallo Clinic & Research Center

University of California
San Francisco

UCSF

Department of Neurology
Memory and Aging Center

Bruce L. Miller, MD
A.W. & Mary Margaret Clausen
Distinguished Chair
Director, Memory and Aging Center
Professor of Neurology & Psychiatry
UCSF School of Medicine

350 Parnassus Avenue, Suite 905
San Francisco, CA 94117
tel: 415/476-5591
fax: 415/476-5573
memory.ucsf.edu
bmiller@memory.ucsf.edu

Mailing Address:
UCSF Box 1207
San Francisco, CA 94143-1207

July 27, 2011

Dear Committee Members,

I strongly support the proposed career development plan of Dr. Joshua Woolley, and his research project that will focus on the behavioral, physiological and neurophysiological effects of intranasal oxytocin in patients with recent onset schizophrenia. Josh's background and skills are ideally suited to his proposed research, and he is certain to make important contributions to the interdisciplinary investigation of social and behavioral neurobiology.

I have known Josh for about 10 years (since he introduced himself as a first-year medical student in 2000) and during this time, he has consistently impressed me with his intelligence, drive and focus. Furthermore, Josh's genuine curiosity and enthusiasm have only grown during his medical training, residency and fellowship. When he started work in my clinic after his first year of medical school, Josh quickly integrated himself into the research team and made immediate contributions by effectively conducting clinical exams. He showed poise uncommon at his stage of training, and his comprehensive and compassionate patient evaluations became an asset to the research group. Furthermore, Josh has a demonstrated ability to build collaborations that tackle complex research questions and a dogged determination to complete important projects.

I witnessed Josh's innovative approach to research when he formally joined my clinical group at the UCSF Memory and Aging Center and began a unique collaboration with Howard Fields' basic neuroscience laboratory. This was the first time a multidisciplinary clinical and basic approach had been attempted for dissertation research at UCSF, let alone so successfully completed. Josh took the lead at every juncture; he envisioned, designed and implemented the elegant study, and his experience on this previous research will be an invaluable foundation for his development as an independent, multidisciplinary investigator.

In this proposed project, Josh will examine the role of oxytocin in social cognition and behavior as well as in the neurophysiological responses to social stimuli in patients with recent-onset schizophrenia. Josh's proposed study will inform our understanding of possible therapeutic role oxytocin could play in patients' positive social behavior through interactions with ventral affective processing system and the parasympathetic nervous system. With his extensive experience of neuroimaging techniques in combination with his psychiatric training, I believe Josh has an exceptional grounding from which to carry out the proposed study and bring the exciting prospect of the development of novel approaches to schizophrenia treatment.

In summary, Dr. Woolley is an excellent clinician and brings a neuroscience perspective to the evaluation of psychiatric patients. His proposal for exploring social behavior and its underlying mechanisms holds promise for developing our

understanding of the fundamental processes of social behavior in both health and disease. He is an outstanding candidate for a Career Development Award and would benefit tremendously from this support while he builds a truly unique skill set to serve him in his career goals.

Sincerely,

Bruce L. Miller, MD
A.W. & Mary Margaret Clausen Distinguished Chair
Director, Memory and Aging Center
Professor of Neurology & Psychiatry
UCSF School of Medicine

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BERKELEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO SANTA BARBARA · SANTA CRUZ

Owen Wolkowitz, M.D.
Professor of Psychiatry
Department of Psychiatry
University of California, San Francisco

Address correspondence to:
401 Parnassus Ave, Box F-0984
San Francisco, CA 94143-0984
Tel: (415) 476-7433 Fax: (415) 502-2661
E-mail: owenw@itsa.ucsf.edu

August 12, 2011

Veteran's Administration
Clinical Sciences Research and Development (CSR&D) Service

Re: Dr. Joshua Woolley

To The Selection Committee,

I am delighted to write a letter of recommendation for Dr. Joshua Woolley, who is applying for a Career Development Award (CDA-2). I believe he is an outstanding candidate for this opportunity. I have known Josh for over five years, first while he was a medical student and then a psychiatry resident at UCSF. We initially became acquainted due to our mutual interest in investigating mechanisms, markers and treatments for major mental illnesses. During his residency, Josh led a study in which we examined the relationships between brain-derived neurotrophic factor (BDNF), biological aging and morphological changes in the brains of dementia patients. Josh designed and implemented this study, analyzed the data and prepared the manuscript largely independently. I was extremely impressed with his ability, energy, motivation, facility with clinical research, autonomy and professionalism.

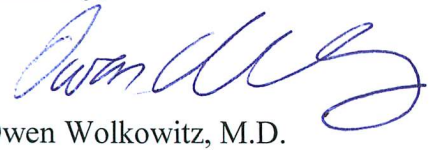
I have also had several opportunities to discuss with Josh his current proposal involving oxytocin (OT) administration to individuals with schizophrenia. Athough a potential role of OT in schziophrenia has been postulated for some years, until recently there were no trials of OT administartion in individuals with schizophrenia, and even now there are not more than a handful of such studies. Josh showed adventurous and well-placed enthusiasm in choosing this potentially high-yield area for research. As part of his prepartaion for this study, he went through the process of obtaining his own IND for intranasal OT administration. I am very impressed with the scientific design of his proposed study, combining Josh's expertise in biochemistry/ psychoneuroendocrinology with his expertise in assessing human emotions and mental processes. In particular, Josh's study will be the first in this population to examine OT effects on naturalistic, ecologically valid social interaction measures, a big advance over standard facial emotion recognition paradigms. The thoughtfullness, authority and forward-thinking with which Josh designed this study are remarkable for someone at his level of training and strengthen my expectation that Josh will become a major figure in psychiatric research.

A particularly unique aspect of Josh's joint MD-PhD background is his in-depth familiarty both with basic neuroscience approaches and psychological/ psychiatric approaches, the latter extending even into psychodynamic perspectives in his research. Although Josh is yet an early career psychiatrist, he has already distinguished himself in many ways and has the capacity to become a leader in the integration of psychological and psychobiological theories. He has been very highly regarded by his teachers and peers at UCSF and has a very impressive publication record. He already has first-authored publications in many of the premier journals in our field, e.g., *American Journal of Psychiatry*, *Neurology*, *Neuroscience*, *Brain Research* and the *Annals of the New York Academy of Sciences*. He is tackling researchable issues at the cutting interface of neurology, psychological theories and behavior, such as the biochemical and neurological underpinnings of appetitive behavior, cognition and sociality. With his very keen intellect, high level of motivation and drive and his outstanding knowledge base, he will make outstanding use of this training opportunity. I believe his research program stands to greatly benefit the VA population of individuals with serious mental illnesses, such as schizophrenia.

I should mention one additional context in which I came to know Josh's abilities. During the last year of his residency at UCSF, I was his clinical caseload supervisor in the Langley Porter Psychiatric Institute (a teaching hospital of UCSF) Adult Outpatient Clinic and met with him weekly during that time. As part of this rotation, he evaluated and treated adult patients with depression, bipolar illness, anxiety disorders and psychotic disorders. He became very proficient in short- and long-term psychotherapies, group therapy and pharmacotherapy. With his "hard science" background, I would have expected Josh to gravitate particularly towards biological formulations and treatment plans, but I was struck by the thoughtfulness and broad-reaching nature of his treatment approaches. He truly endorses a multi-faceted view of personality, development and psychopathology.

In summary, I think very highly of Josh and expect great things of him. He is on his way to becoming a super star, and the opportunity afforded him by this training grant will strengthen and help shape his future development as a major contributor to our field. I recommend him very highly.

Sincerely,



Owen Wolkowitz, M.D.
Professor of Psychiatry

Electronic Submission Checklist

(Revised 01/31/11)

Downloading Application Packages from Grants.gov

☒ Is the application package from the correct/intended R&D Service?

☒ Does the application package correspond to the correct RFA for the Service?

☐ Unless instructed otherwise: If this is a resubmission, does the R&D Service and RFA name match the previous Summary Statement?

*Note: Application packages are R&D Service- **and** RFA-specific.*

*The application package for an RFA issued by one R&D Service may **not** be used to submit an application to a different Service, even if they are for the same ORD-Wide Program Announcement.*

*Within an R&D Service, the application package for one RFA may **not** be used to submit an application to a different RFA.*

Applications that are not responsive to an RFA will be administratively withdrawn/not accepted for review.

Completing the SF-424 Cover Component

☐ If this is a resubmission, did you use **your** Application Number (i.e., **BX000999)** from the previous Summary Statement in Box 4a? **Do NOT include any other portion of the previous number (i.e., I01- or -01A1**)

☒ Did you include the Agency Routing Number in Box 4b?

☒ Is the Descriptive Title (Cover Component, item 11) **81 characters or less (including spaces and punctuation)**?

☒ Does the Descriptive Title match the title approved in the ITS or LOI process (HSR&D or RR&D, respectively)?

☒ Are the Start and End Dates (Cover Component, item 12) correct for the proposed work?

*Note: **Titles in excess of 81 characters (including spaces and punctuation) will be truncated** by eRA Commons and will not be restored by VA-ORD staff. **Proposals with truncated titles may not be accepted for review.***

Completing the SF-424 Other Project Information Component

☒ Did you correctly indicate the use of human subjects and/or animals (items 1 and 2)?

☒ Did you provide the correct Federal Assurance Number(s) (items 1a and 2a) if required?

☒ Did you attach **separate** documents for the Project Summary/Abstract (item 7; 40 lines max) and the Project Narrative (item 8; relevance statement; 10 lines max)? **Do not duplicate contents**.

☒ Is the Director's Letter included in a separate attachment (**08_VA_Director_Letter.pdf**)?

☐ Have you included a copy of all necessary waiver approvals (budget cap, off-site, etc.) with the Letters of Support (**08a_VA_Letters.pdf**)?

Completing the SF-424 Budget Component

☒ Did you submit a set of budget pages for **all** of the funding periods (e.g., **one set per year**)?

☒ Is the proposed budget within the limits (**annual budget cap, duration, etc**) stated in the RFA?

☐ If you used a Subaward Component **or Appendix** to submit budget additional sites, does Section F, Line 5 of the Budget list the aggregate/total cost of all the site budgets?

☐ If you used a Subaward Component **or Appendix**, did you attach a **separate** budget justification to the budget pages for each additional site? **Do not** attach the primary site budget justification to each site budget.

Completing the SF-424 Application Package - General

☒ Has a Page 18 been completed for **all PD/PIs** and does it include their eRA Commons ID (CID)?

☒ Did you include the eRA Commons ID (CID) for **all PD/PIs** on the Senior/Key Person Profile component?

☒ Do the CIDs on the Page 18s match the CIDs used on the Senior/Key Personnel component?

Note: Applications that do not contain a CID for all PD/PI's cannot be processed by eRA Commons and no e-mails concerning the status (warning and/or errors) of the application will be sent.

There are separate VA deadlines for (1) submission to Grants.gov and (2) verification in eRA commons.

Submissions that miss either deadline are considered late and will not be accepted for review.

Be sure to submit early enough to make any necessary corrections and submit all Changed/Corrected applications before the stated deadlines (Check each RFA for correct deadlines).

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: Joshua | Middle Name:
* Last Name: Woolley | Suffix:
Position/Title: Research Fellow | Department: Psychiatry
Organization Name: San Francisco Veterans Affairs Medical Center | Division: Mental Health
* Street1: 4150 Clement Street
Street2: 116C-1
* City: San Francisco | County/ Parish:
* State: CA: California | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 941211545
* Phone Number: 415-722-6662 | Fax Number:
* E-Mail: josh.woolley@ucsf.edu

Credential, e.g., agency login: joshwoo

*** Project Role:** PD/PI | **Other Project Role Category:**

Degree Type: MD/PhD
Degree Year: 2007

***Attach Biographical Sketch** 1234-Woolley,Joshua_Bio for C [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support 1235-Woolley_other_support.pd [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 1

Prefix: Dr. | * First Name: Daniel | Middle Name:
* Last Name: Mathalon | Suffix:
Position/Title: Staff Psychiatrist | Department: Psychiatry
Organization Name: San Francisco Veterans Affairs Medical Center | Division: Mental Health
* Street1: Building 8 Rm 9B
Street2: 4150 Clement St.
* City: San Francisco | County/ Parish:
* State: CA: California | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 941211545
* Phone Number: 415-221-4810x3860 | Fax Number:
* E-Mail: daniel.mathalon@ucsf.edu

Credential, e.g., agency login: DANIELMATHALON

*** Project Role:** Other (Specify) | **Other Project Role Category:** Co-mentor

Degree Type: MD/PhD
Degree Year: 1994

***Attach Biographical Sketch** 1236-Mathalon_biosketch.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support 1237-Mathalon_other_support.p [Add Attachment] [Delete Attachment] [View Attachment]

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2

Prefix: Dr. * First Name: Wendy Middle Name: Berry

* Last Name: Mendes Suffix:

Position/Title: Sarlo/Ekman Associate Professor Department: Psychiatry

Organization Name: University of California, San Francisco Division:

* Street1: 401 Parnassus Avenue

Street2:

* City: San Francisco County/ Parish:

* State: CA: California Province:

* Country: USA: UNITED STATES * Zip / Postal Code: 94143-0984

* Phone Number: 415-476-8839 Fax Number:

* E-Mail: wendy.mendes@ucsf.edu

Credential, e.g., agency login: WBMENDES

*** Project Role:** Other (Specify) **Other Project Role Category:** Co-mentor

Degree Type: PhD

Degree Year: 2003

***Attach Biographical Sketch** 1238-Mendes_biosketch.pdf Add Attachment Delete Attachment View Attachment

Attach Current & Pending Support 1239-Mendes_other_support.pdf Add Attachment Delete Attachment View Attachment

PROFILE - Senior/Key Person 3

Prefix: Dr. * First Name: Kate Middle Name:

* Last Name: Rankin Suffix:

Position/Title: Associate Professor in Residence Department: Memory and Aging Center

Organization Name: University of California, San Francisco Division:

* Street1: Box 1207

Street2: 350 Parnassus Avenue 502

* City: San Francisco County/ Parish:

* State: CA: California Province:

* Country: USA: UNITED STATES * Zip / Postal Code: 94143-1207

* Phone Number: 415-502-0619 Fax Number: 415-476-0213

* E-Mail: krankin@memory.ucsf.edu

Credential, e.g., agency login: krankin

*** Project Role:** Other (Specify) **Other Project Role Category:** Co-mentor

Degree Type: PhD

Degree Year: 2000

***Attach Biographical Sketch** 1240-Rankin_biosketch.pdf Add Attachment Delete Attachment View Attachment

Attach Current & Pending Support 1241-Rankin_other_support.pdf Add Attachment Delete Attachment View Attachment

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 4

Prefix: Dr. * First Name: Sophia Middle Name:
* Last Name: Vinogradov Suffix:
Position/Title: Interim Associate Chief of Staff Department: Psychiatry
Organization Name: San Francisco Veterans Affairs Medical Center Division: Mental Health
* Street1: Box 116C
Street2: VAMC
* City: San Francisco County/ Parish:
* State: CA: California Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 94143-116C
* Phone Number: 415-221-4810x3106 Fax Number:
* E-Mail: sophia.vinogradov@ucsf.edu

Credential, e.g., agency login: VINOGRADOV

*** Project Role:** Other (Specify) **Other Project Role Category:** Primary Mentor

Degree Type: MD
Degree Year: 1983

***Attach Biographical Sketch** 1242-Vinogradov_biosketch.pdf Add Attachment Delete Attachment View Attachment
Attach Current & Pending Support 1243-Vinogradov_other_support Add Attachment Delete Attachment View Attachment

PROFILE - Senior/Key Person 5

Prefix: Dr. * First Name: Sue Middle Name:
* Last Name: Carter Suffix:
Position/Title: Professor Department: Psychiatry
Organization Name: University of Illinois at Chicago Division:
* Street1: 1601 W. Taylor St. MC 912
Street2:
* City: Chicago County/ Parish:
* State: IL: Illinois Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 60612-7342
* Phone Number: 312-355-1593 Fax Number:
* E-Mail: scarter@psych.uic.edu

Credential, e.g., agency login: SCARTER

*** Project Role:** Other (Specify) **Other Project Role Category:** O.S.C (Consultant)

Degree Type: PhD
Degree Year: 1969

***Attach Biographical Sketch** 1244-Carter_biosketch.pdf Add Attachment Delete Attachment View Attachment
Attach Current & Pending Support Add Attachment Delete Attachment View Attachment

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 6

Prefix: Dr. * First Name: David Middle Name:
* Last Name: Leitman Suffix:
Position/Title: Research Assistant Professor Department: Cognitive Neuroscience
Organization Name: University of Pennsylvania Division:
* Street1: Gates Pavilion 10th Floor Rm 1016
Street2: 3400 Spruce St.
* City: Philadelphia County/ Parish:
* State: PA: Pennsylvania Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 19104-4283
* Phone Number: 215-662-7389 Fax Number:
* E-Mail: leitman@mail.med.upenn.edu

Credential, e.g., agency login: DILEITMAN

*** Project Role:** Other (Specify) **Other Project Role Category:** O.S.C (Consultant)

Degree Type: PhD
Degree Year: 2006

***Attach Biographical Sketch** 1245-Leitman_Biosketch.pdf Add Attachment Delete Attachment View Attachment
Attach Current & Pending Support Add Attachment Delete Attachment View Attachment

PROFILE - Senior/Key Person 7

Prefix: Dr. * First Name: Steven Middle Name:
* Last Name: Porges Suffix:
Position/Title: Professor Department: Psychiatry
Organization Name: University of Illinois at Chicago Division:
* Street1: 1601 W. Taylor St.
Street2:
* City: Chicago County/ Parish:
* State: IL: Illinois Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 60612-7342
* Phone Number: 312-355-1557 Fax Number:
* E-Mail: sporges@uic.edu

Credential, e.g., agency login: sporges

*** Project Role:** Other (Specify) **Other Project Role Category:** O.S.C (Consultant)

Degree Type: PhD
Degree Year: 1970

***Attach Biographical Sketch** 1246-Porges_biosketch.pdf Add Attachment Delete Attachment View Attachment
Attach Current & Pending Support Add Attachment Delete Attachment View Attachment

BIOGRAPHICAL SKETCH

NAME **Joshua D. Woolley, MD, PhD**	POSITION TITLE VA Advanced Neuroscience Research Fellow
eRA COMMONS USER NAME JOSHWOO	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Brown University, Providence, RI	BS	1995-1999	Biology/Philosophy of Science
University of California San Francisco, SF, CA	MD	2000-2007	Medicine
University of California San Francisco, SF, CA	PhD	2002-2005	Neuroscience
University of California San Francisco, SF, CA	Residency	2007-2011	Psychiatry

A. Personal Statement: The goal of the proposed research is to investigate the effects of intranasal oxytocin on social behavior and neural functioning in patients with schizophrenia. Specifically, I plan to quantify the effects of exogenous oxytocin in patients with schizophrenia on, 1) social cognitive abilities as measured by well-validated social cognitive tasks, 2) neural responses to social stimuli using functional brain imaging, and 3) social behavior and physiology during an ecologically valid, laboratory-based dyadic interaction. I have the expertise, leadership and motivation necessary to successfully carry out the proposed work. As a graduate student, I forged a unique collaboration between a clinical research laboratory and a basic neuroscience laboratory, successfully leading both human and animal studies focused on the neurohormonal determinants of behavior. As a psychiatry resident, I learned how to carefully categorize social and non-social behavior, and I learned how to diagnose various psychiatric illnesses. As a research fellow, I have developed a program of research focused on the investigation of the psychological, behavioral, physiological and neural effects of intranasal oxytocin in patients with severe mental illness. To this end, I am currently running several studies investigating the effects on oxytocin on social cognition, behavior and physiology in patients with schizophrenia and their families. In addition, I have successfully administered several clinical studies (e.g. staffing, research protections, budget), collaborated with other researchers, and produced several peer-reviewed publications from each project. As a result of my previous experiences, I am aware of the importance of constructing a realistic research plan, timeline, and budget. While my training positions me to successfully complete the proposed studies, to become an independent academic researcher, I must develop further expertise in neuroimaging methods, advanced statistics and psychophysiology. My long-term goals are to pursue an academic career in psychiatric neuroscience within the Veteran's Affairs health system, incorporating insights from the bedside and performing clinical and basic research. I hope to use breakthroughs from behavioral neuroscience in animals and insights from clinical experience to inform my behavioral, cognitive and hormonal research on social behavior in patients. In sum, my extensive training in clinical psychiatry and neuroscientific research methods and my need for further training make me ideally suited to receive and benefit from a career development award.

Percent Effort: 75% Research 20% Clinical 5% teaching/mentoring and 0% administration

B. Positions and Honors

Honors and Awards

1996 - 1998	Three-time recipient of the Research At Brown prize, Brown University
1998	Undergraduate Teaching Research Award, Brown University
1999	Undergraduate Hughes fellowship, Brown University
1999	Weston prize for excellence in Psychology and Developmental Biology, Brown University
1999	John Wellington prize for excellence in Metaphysics, Brown University
1999	Graduated Suma Cum Laude, Brown University
1999 - 2000	Fulbright Scholarship to Karolinska Institutet, Stockholm, Sweden
1999	Goldwater Prize for Excellence in Science and Mathematics, Brown University

2008 The Alzheimer's Association's Kathryn Grupe Award for Excellence in Alzheimer's Research, Honorable Mention
2008 American Psychiatric Institute for Research Education, Jansen scholar
2009 Named "Everyday Hero" for outstanding care in a particularly difficult clinical case
2009 Scholarship to attend invitation-only '2009 Obesity and Food Addiction Summit,' Bainbridge Island, WA
2010– 2011 American Psychoanalytic Association Fellowship
2010 Clinical and Translational Science Insitute at UCSF Resident Travel Award
2011 Robert Wood Johnson Foundation Health and Society Scholar Fellow, Columbia University (declined)

Positions and Employment

1995 - 1999 Research Assistant, Brown University
2005 - 2009 Research Fellow, Memory and Aging Center, UCSF
2007- 2011 Resident Physician, Department of Psychiatry, UCSF
2011- present VA Advanced Neuroscience Research Fellow, SFVAMC

Professional Memberships

2008-present American Psychiatric Association

B. Selected Peer-Reviewed Publications

1. Woolley JD. The functional morphology of the avian flight muscle M. Coracobrachialis posterior. J Exp Biol. 2000; 203(11): 1767-76.
2. Woolley* JD, Svensson* E, Wikström M, and Grillner S. Endogenous dopaminergic modulation of the lamprey spinal locomotor network. Brain Res. 2003 Apr 25; 970(1-2): 1-8.
3. Woolley JD. Buccofacial apraxia and the expression of emotion. Ann N Y Acad Sci. 2003; 1000: 395-401.
4. Gorno-Tempini ML, Rankin KP, Woolley JD, Rosen HJ, Phengrasamy L, Miller BL. Cognitive and behavioral profile in a case of right anterior temporal lobe neurodegeneration." Cortex. 2004; 40(4-5): 631-44.
5. Woolley JD, Gorno-Tempini ML, Werner K, Rankin KP, Ekman P, Levenson RW, and Miller BL. The autonomic and behavioral profile of emotional dysregulation. Neurology, 2004; 63(9): 1740-3.
6. Taha SA, Norsted E, Lee LS, Lang PD, Lee BS, Woolley JD, and Fields HL. Endogenous opioids encode relative taste preference. Eur J Neurosci, 2006; 24(4): 1220-6.
7. Woolley JD, Lee BS, and Fields HL. Nucleus accumbens opioids regulate flavor-based preferences in food consumption. Neuroscience, 2006; 17(143(1)): 309-17.
8. Woolley JD, Lee BS, Taha SA, and Fields HL. Nucleus accumbens opioid signaling conditions short-term flavor preferences. Neuroscience, 2007; 146(1): 19-30.
9. Woolley JD, Lee BS, Kim B, and Fields HL. Opposing effects of intra-nucleus accumbens mu and kappa opioid agonists on sensory specific satiety. Neuroscience, 2007; 146(4): 1445-52.
10. Woolley JD, Gorno-Tempini ML, Seeley WW, Rankin KP, Lee SS, Matthews BR, Miller BL. Binge eating is associated with right orbitofrontal-insular-striatal atrophy in frontotemporal dementia. Neurology, 2007 Oct 2; 69(14):1424-33.
11. Woolley JD, Wilson MR, Hung E, Gorno-Tempini ML, Miller BL, Shim J. Frontotemporal Dementia and Mania. Am J Psychiatry. 2007 Dec; 164(12):1811-6. PMID: 18056235.
12. Woolley JD, Khan BK, Murthy NM, Miller BL, Rankin KP. Rates of and risk factors for psychiatric misdiagnosis in patients with early neurodegenerative disease. J. Clin. Psychiatry. 2011 Feb;72(2):126-33.
13. Woolley JD, Douglas VC Cree, BAC. Neuromyelitis optica and primary polydipsia: a case report. Gen Hosp Psychiatry, 2010 Nov-Dec; 32(6):648.e5-8.
14. Woolley JD, Strobl EV, Shelly WB, Miller BL, Wolkowitz OM, Mellon SH Rankin KP. BDNF serum concentrations show no relationship with diagnostic group or medication status in neurodegenerative disease. Curr. Alzheimer Res. 2011 May 24. [Epub ahead of print].
15. Khan BK, Woolley JD, Chao S, See T, Karydas AM, Miller BL, Rankin KP. Schizophrenia or neurodegenerative disease prodrome? Outcome of a first psychotic episode in a 35-year old woman. Psychosomatics. In Press.

C. Research Support:

Current

(Woolley) 9/1/2011 – 9/1/2012
UCSF San Francisco Treatment Research Center: Pilot Study Program
The Effects of Intranasal Oxytocin on Social Cognition and Social Approach Behaviors in Opioid-dependent Patients receiving Methadone Treatment

This grant will pay for a preclinical trial of using intranasal oxytocin to improve social cognition and promote sociality in opioid-dependent patients on methadone treatment. Role: Principal Investigator.

(Weiss) 1/1/2011 – 1/1/2012
UCSF Research Evaluation and Allocation Committee Pilot Research Grant
Oxytocin and Unhealthy Interactions in Families of Patients with Recent Onset Schizophrenia: A Novel Biomarker

This grant will pay for a preclinical trial of using intranasal oxytocin to improve interpersonal interactions in families with a child with recent-onset schizophrenia. Role: Co-Investigator.

(Woolley) 7/1/2010 – 7/1/2012
UCSF Collaborative Translational Pilot Rsch Grants in Child & Adolescent Mental Disorders
The Potential of Oxytocin as a Biomarker and Adjunct Therapy for Adolescents with First-Episode Schizophrenia

This grant will pay for a preclinical trial of using intranasal oxytocin to improve social cognitive deficits in adolescents with recent-onset schizophrenia. Role: Principal Investigator.

Completed

R25 MH060482 (Reus) 7/23/2000 – 6/30/2011
NIH/National Institute of Mental Health
Training the Next Generation of Mental Health Researchers

This grant seeks to increase the number and quality of clinical research investigators in mental health through proactive and collaborative mentorship & targeted research support. It will facilitate the development of translational research through the collaborative involvement and mentorship of prospective trainees by researchers active in basic neuroscience and clinical behavioral research. It is funding for protected research time for research track residents at UCSF. During their third year, residents have 30% protected time and during their fourth year they have 90% protected time. Role: Psychiatric Resident Research Fellow (started at 7/01/2007).

(Woolley) 5/1/2010 – 5/1/2011
UCSF Resident Clinical & Translational Rsch Funding Grant
Hormonal alterations in frontotemporal dementia
This grant will pay for hormonal assays of blood from patients with neurodegenerative disease including fronto-temporal dementia. Role: Principal Investigator.

(Woolley)
UCSF Resident Clinical & Translational Rsch Funding Grant 5/1/2008 – 4/30/2009
Reward Processing in Frontotemporal dementia

This grant was used to support research of temporal processing in patients with neurodegenerative disease including fronto-temporal dementia. Role: Principal Investigator.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Daniel H. Mathalon	UCSF title: Professor in Residence VA title: Staff Psychiatrist
eRA COMMONS USER NAME DANIELMATHALON	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of California, Berkeley, CA	AB	9/81-8/83	Psychology
Indiana University, Bloomington, IN	PhD	9/84-12/91	Psychology
Stanford University	MD	9/89-6/94	Medicine
Stanford University	Residency	7/94-6/98	Psychiatry
Stanford University	Fellowship	7/97-6/99	Psychophysiology
Diplomate in Psychiatry		2000	

A. Personal Statement

I am a co-mentor on the proposed CDA. I am trained as a clinical psychologist and a psychiatrist whose research uses EEG, event-related potentials, and functional MRI to study the pathophysiology underlying the symptoms and course of schizophrenia. A major focus of my laboratory currently is to identify neurophysiological markers of risk for psychosis that can improve our ability to predict which patients at clinical high risk for psychosis based on prodromal symptoms will go on to convert to a full-blown psychotic disorder. I am the Director of Neuroimaging of the Prodromal Assessment, Research, and Treatment (PART) program at UCSF. I also collaborate with other faculty by applying his ERP and fMRI expertise to other clinical domains including compulsive hoarding, post-traumatic stress disorder, chronic pain, and treatment-resistant depression. I have research funding from NIMH and the NARSAD foundation. For the past two years, I have served as Director of the Resident Research Track at UCSF, facilitating the recruitment and training of psychiatry residents interested in pursuing research careers. I have also mentored numerous psychiatry residents (including Dr. Woolley) and psychology fellows over the past decade, with many of my mentees successfully competing for NARSAD grants and securing faculty positions in psychology or psychiatry departments around the country. I have extensive experience and expertise in the design and analysis of functional neuroiming studies. This expertise will allow me to successfully mentor Dr. Woolley on the neuroimaging portion of his proposed studies.

Time and Effort Statement

Research: 25%, Clinical: 37.5%, Administration: 12.5%, Teaching: 25%

B. Positions and Honors

Positions and Employment

1999 – 2000 Senior Research Psychiatrist, SRI International; Menlo Park, CA
2000 – 2006 Assistant Professor, Department of Psychiatry, Yale University
2000 – 2007 Staff Psychiatrist, Veterans Affairs Connecticut Healthcare System, West Haven
2006 – 2007 Associate Professor, Department of Psychiatry, Yale University
2008 – 2010 Associate Professor, Department of Psychiatry, University of California, San Francisco
2008 – present Staff Psychiatrist, San Francisco VA Medical Center
2010 – present Professor in Residence, Department of Psychiatry, University of California, San Francisco

Other Experience and Professional Memberships

1996 – present Member, American Psychiatric Association (APA)
1998 – present Member, Society for Psychophysiological Research
1999 – present Member, Society of Biological Psychiatry
2003 – present Associate member, American College of Neuropsychopharmacology
2008 – present Member, NIMH Study Section, NIH/ZRG1-NPAS (03) Review Committee
2010 – present Member, American College of Neuropsychopharmacology

Honors

1983 A.B. summa cum laude and highest departmental honors; Departmental Citation in

	Psychology, UC Berkeley; Phi Beta Kappa; Psi Chi (Psychology honorary)
1986	Ph.D. Qualifying Exam Commendations; Edwards Fellowship, Indiana University
1989	Member, Sigma Xi
1997	Young Investigator Travel Award, International Congress on Schizophrenia Research
1998	Laughlin Fellowship, American College of Psychiatrists; Lilly Travel Award, Society of Biological Psychiatry; APA Lilly Resident Research Award; APA Junior Investigator Research Colloquium
1999	Bristol-Myers Squibb Travel Fellowship, ACNP
2003	Early Career Contribution Award, EEG Clinical Neuroscience Society
2004 & 2006	Senior Scientist Award, Biennial Winter Workshop on Schizophrenia
2005	Kempf Award, American Psychiatric Association

C. Selected peer-reviewed publications (in chronological order)

Most relevant to the current application

1. Yun RJ, Krystal JH, Mathalon DH (2010). Working memory overload: fronto-limbic interactions and effects on subsequent working memory function. *Brain Imaging Behav*. 4(1):96-108. PMCID: PMC2854358.
2. Li CS, Krystal JH, Mathalon DH (2005). Fore-period effect and stop-signal reaction time. *Exp Brain Res*, 167(2), 305-9.
3. Roach, B.J., **Mathalon, D.H.** Event-related EEG time-frequency analysis: An overview of measures and anlysis of early gamma band phase locking in schizophrenia. *Schiz Bulletin*, 2008, 34(5), 907-26.
4. Mathalon DH, Hoffman RE, Watson TD, Miller RM, Roach BJ, Ford JM (2010). Neurophysiological Distinction between Schizophrenia and Schizoaffective Disorder. *Frontiers in Human Neuroscience*. 29;3:70. PMCID: PMC2816168.
5. Watson, T.D., Petrakis, I.L., Edgecombe, J., Perrino, A., Krystal, J.H., **Mathalon, D.H.** Modulation of the cortical processing of novel and target stimuli by drugs affecting glutamate and GABA neurotransmission. *International Journal of Neuropsychopharmacology*, 2009, 12(3), 357-70.

Additional recent publications of importance to the field

1. Mathalon, DH, Sullivan, EV, Rawles, JM, & Pfefferbaum, A (1993). Correction for head size in brain imaging measurements. *Psychiatry Research: Neuroimaging, 50,* 121-39.
2. Mathalon DH, Ford JM, Rosenbloom MJ, & Pfefferbaum A (2000): P300 reduction and prolongation with illness duration in schizophrenia. *Biol Psychiatry, 47,* 413-27.
3. Mathalon DH, Ford JM, & Pfefferbaum A (2000). Trait and state aspects of auditory P300 amplitude reduction in schizophrenia: a longitudinal study. *Biol Psychiatry, 47,* 434-49.
4. Mathalon, DH, Sullivan,EV, Lim,KO, Pfefferbaum,A (2001). Progressive brain volume changes and the clinical course of schizophrenia in men: A longitudinal MRI study*. Arch Gen Psych, 58,* 148-57.
5. Mathalon DH, Fedor M, Faustman WO, Gray EM, Askari N, Menon V & Ford JM (2002). Response-monitoring dysfunction in schizophrenia: An event-related brain potential study*. J Ab Psychol, 111(1)*, 22-41.
6. Mathalon, DH, Faustman, WO, & Ford, JM (2002). N400 and thought disorder in schizophrenia. N400 and automatic semantic processing abnormalities in patients with schizophrenia. *Arch Gen Psych*, *59*, 641-8.
7. Mathalon, DH, & Ford, JM (2002). The long and the short of it: Influence of interstimulus interval on auditory P300 abnormalities in schizophrenia. *Clinical EEG, 33(3)*, 125-35.
8. Mathalon, DH, Pfefferbaum, A, Lim, KO, Rosenbloom, MJ, & Sullivan, EV (2003). Compounded brain volume deficits in schizophrenia-alcoholism comorbidity. *Arch Gen Psych,* 60, 245-52.
9. Mathalon, DH, Heinks, T, Ford JM (2004). Selective attention in schizophrenia: Sparing and loss of executive control. *Am J Psychiatry,* 161(5), 1-12.
10. Mathalon DH, Jorgensen KW, Roach BJ, Ford JM (2009). Error detection failures in schizophrenia: ERPs and FMRI. 73(2):109-17. DOI: 10.1016/j.ijpsycho.2009.02.005; PMID: 19414043.

C. Research Support

Ongoing

R01 MH076989 (Mathalon) 5/21/2007 – 4/30/2012
NIH/National Institute of Mental Health
Functional brain abnormalities in the schizophrenia prodrome

This study proposes to use fMRI and ERP measures of sensory processing, attention, and working memory to assess abnormalities in patients meeting criteria for the prodromal syndrome who are at ultra-high risk for development of schizophrenia. Prodromal patients will be compared with early illness

schizophrenia patients and healthy controls on these functional brain measures. In addition, prodromal patients will be followed clinically over two years to examine whether ERP and/or fMRI measures of compromised brain function predict subsequent conversion to schizophrenic psychosis. Role: Principal Investigator.

R01 AT004572 (Eisendrath) 4/01/2008 – 2/28/2013
NIH/National Ctr. For Complementary & Alternative Medicine
Applying Mindfulness-Based Cognitive Therapy to Treatment-Resistant Depression
In the currently proposed revision (supplement) to the parent R01 study, we are responding to NIH calls for increased biological understanding of therapeutic interventions. We propose to enroll 80 participants from the R01 to receive fMRI assessments immediately before and after the 8-week MBCT+TAU or HEP+TAU interventions. We propose to implement both emotion regulation (affect labeling) and emotional interference during executive control (emotional working memory) tasks during fMRI scanning to probe the ventral affective processing and dorsal executive control systems before and after the eight weeks of MBCT or HEP. The results will have public health benefits both by identifying an effective treatment for TRD, and elucidating the neural mechanisms associated with MBCT. Role: Co-PI and PI of SF VAMC NCIRE subcontract.

U24 RR021992 (Potkin) 2/8/2006 – 11/30/2011
NIH/ National Center for Research Resources
Function BIRN
Participate in a multi-site project to develop and validate fMRI for large-scale multi-site studies of schizophrenia. Role: Investigator (UCSF Site).

R01 MH081051 (Vinogradov) 4/1/2008 – 3/31/2013
NIH/National Institute of Mental Health
Neuroscience-Guided Cognitive Remediation in Adolescents at Risk for Psychosis
In this study, individuals in the “prodrome” or ultra high risk (UHR) phase of schizophrenia will participate in neuroplasticity-based cognitive training exercises in order to 1) “rescue” UHR individuals *before* the brain has experienced a first episode of psychosis and undergone what may be deleterious and/or irreversible changes in cortical operations, and 2) prevent or attenuate the onset of psychotic disorder and improve long-term adaptive functioning in these UHR adolescents. Role: Co-Investigator.

R01 MH082818 (Vinogradov) 8/01/2009 – 4/30/2014
NIH/ National Institute of Mental Health
Optimizing Cognitive Remediation Outcomes in Schizophrenia
Role: Investigator

R01 MH058262 (Ford) 8/1/1998 – 6/30/2013
NIH/ National Institute of Mental Health
Corollary Discharge Dysfunction in Schizophrenia: ERPs and EEG
Use ERPs and EEG to study a dysfunction of a basic neurophysiological mechanism in schizophrenic patients. Role: Investigator

U01 MH082022 (Woods) 9/30/2008 – 4/30/2013
NIH/National Institute of Mental Health
8/8-Predictors and Mechanisms of Conversion to Psychosis
The major goals of this project are to identify predictors and mechanisms of conversion to pschosis in a new sample. Role: Investigator

R21 MH087748 (Mathews) 6/01/2010 – 2/28/2012
NIH/ National Institute of Mental Health
Identifying Intermediate Phenotypes for Compulsive Hoarding
The aim of this application is to conduct a pilot study of work to examine frontally-mediated neurocognitive function in severe compulsive hoarding (SCH), a maladaptive social behavior that is related to obsessive compulsive disorder (OCD) and like OCD, has a complex genetic etiology, with the ultimate goal of identifying intermediate phenotypes that will be useful for genetic studies. Our data suggest that individuals with SCH also have impairments or abnormalities in neuropsychological measures of executive function and in the ERN. We hope to identify potentially useful intermediate neurocognitive phenotypes. Role: Principal Investigator of SFVAMC subcontract.

UCI Subcontract (Potkin) 3/01/2010 – 3/01/2012
Ortho-McNeil Jannsen
Contrasting the Brain Effects of Risperdal and Invega with fMRI and PET Scanning
The objective of this protocol is to compare the brain effects of Invega to Disperdal in patients with schizophrenia, focusing on fMRI BOLD signal difference in response to multiple paradigms. Role: Investigator

N01 DA185550 (Hinshaw) 5/01/2010 – 4/30/2012
NIH/NIDA
Multimodal Treatment Study of Children with ADHD (MTA) - Follow-up (ARRA Supp. to Base Contract)
The MTA is a six-site, cooperative agreement, now focused on long-term follow-up of 579 young adults with ADHD, Combined type, and 289 local normative comparison subjects. The ARRA Supplement funds (a) intensified sample retention efforts, (b) a mixed-method investigation of young adult subject perceptions of turning points in their lives, and (c) neurocognitive assessment and neuroimaging of a subgroup with particular histories of substance abuse across the longitudinal span of the study. Role: Investigator and PI of NCIRE subcontract with UC Berkeley.

(McCaslin) 12/1/2008 – 4/30/2012
Department of Defense
fMRI of PTSD and Chronic Pain Comorbidity
This study examines functional brain abnormalities in patients with comorbid post-traumatic pain disorder and chronic pain. Role: Investigator

Completed in the Last Three Years

(Mathalon) 9/15/2008 – 9/14/2011
NARSAD
Functional Brain Changes Following Cognitive Remediation
This Independent Investigator Award uses fMRI to track improvements in brain function in patients with first episode schizophrenia undergoing cognitive remediation training for cognitive dysfunction, in a controlled clinical trial. Role: Principal Investigator

No assigned number (Mathalon/Ford) 09/01/06 – 08/31/10
AstraZeneca
Clinical Translational Neuroscience Studies of Schizophrenia
This study develops and validates electroencephalographic (EEG) indices of sensory, perceptual, and neurocognitive processes that 1) can be readily measured in both human and non-human primates, 2) area sensitive to the pathophysiology of schizophrenia, and 3) area similarly disrupted in both human and non-human primates by NMDA antagonist, ketamine. Role: Co-Principal Investigator.

R21 DA020750 (D'Souza) 8/20/07 – 07/31/09
NIH/National Institute on Drug Abuse
Cannabinoids, Neural Synchrony and Information Processing
The aim of this project is to characterize the effects of cannabinoids on electrical communication within the brain (neural synchrony) using EEG in healthy humans and to relate these effects to their behavioral and cognitive effects. Role: Consultant

Alcohol Beverage Medical Research Foundation (Mathalon) 02/01/05 – 01/31/09
Automatic Processing of Alcohol Cues in Chronic Alcoholism
The major goal of this study, funded by the Alcoholic Beverage Medical Research Foundation, is to use event-related brain potentials (ERP) and functional magnetic resonance imaging (fMRI) to compare the automatic attentional processing of alcohol picture cues in alcoholic subjects who are current drinkers, recently detoxified, or long-term sober. Role: Principal Investigator.

AstraZeneca Pharmaceuticals (Mathalon) 09/01/06 - 02/28/09
Clinical Translational Neuroscience Studies of Schizophrenia
This study developed and validated electroencephalographic (EEG) indices of sensory, perceptual, and neurocognitive processes that 1) can be readily measured in both human and non-human primates, 2) are sensitive to the pathophysiology of schizophrenia, and 3) are similarly disrupted in both human and non-human primates by NMDA antagonist, ketamine. Role: Principal Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Wendy Berry Mendes	POSITION TITLE Sarlo/Ekman Associate Professor of Psychiatry UC San Francisco
eRA COMMONS USER NAME WBMENDES	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
CSU Long Beach	BA/BS/MA	1993/1995	Psychology/Quant Psychology
University of California, Santa Barbara	Ph.D.	2003	Social Psychology
University of California, San Francisco	Post-doc	2004	Psychology & Medicine

A. Personal Statement

I am a co-mentor on the proposed CDA. From 2004-2010, I was a professor of psychology at Harvard University where I directed the Emotion, Health and Psychophysiology Lab. In the fall of 2010 I accepted a position at UC San Francisco where I am the Sarlo/Ekman endowed chair in the study of Human Emotion. I conduct research at the intersection of social and biological psychology, specifically how emotions, stress and motivation are manifested in changes in neural and peripheral responses, and how these changes influence behavior, person perception, and decision making. I have been a PI, co-PI or investigator on 8 projects funded by the National Institutes of Health and have successfully mentored numerous undergraduate, graduate and post-graduates students, many of whom now hold academic positions. My expertise in autonomic measurement and analysis as well as in the study of social and emotional behavior makes me an ideal co-mentor for Dr. Woolley as he completes his training program.

B. Positions and Honors

Employment

2004 – 2008 Assistant Professor of Psychology, Harvard University
2008 – 2010 John L. Loeb Associate Professor of Social Sciences, Harvard University
Core faculty Robert Wood Johnson Health & Society Scholars
Affiliated faculty Center on the Developing Child

2010-present Sarlo/Ekman Associate Professor of Human Emotion
Director of the Emotion, Health, and Psychophysiology Lab
Co-director of the Psychology & Medicine post-doctoral training program
Core faculty NIMH pre-doctoral training program in Affective Science
Affiliated faculty Robert Wood Johnson Health & Society Scholars

Other Experience and Professional Memberships

1999 – Present American Psychological Society
1999 – Present American Psychological Association
1999 – Present Society for Psychophysiological Research
1999 – Present Society for Personality and Social Psychology
2004 – Present Emotion Research Group
2006 – Present Editorial Board Member: Journal of Experimental Social Psychology
2007 – Present Society for the Psychological Study of Social Issues
2009 – Present Editorial Board Member: Psychological Science

2009 – Present	Editorial Board Member: Psychological Bulletin
2009 – Present	Fellow of the Society for Experimental Social Psychology
2009 – Present	Associate Editor: Journal of Personality and Social Psychology: PPID
2011 – Present	Associate Editor: Emotion Review
2011 – Present	Editorial Board Member: Journal of Experimental Psychology: General

Selected Honors

2006	Harvard Research Award for junior faculty
2006-2010	One of Harvard Undergraduates' "Favorite Professors"
2007	Winner of the Gordon Allport Intergroup Relations Prize for best paper on Intergroup Relations
2009	Mentored the "Best graduate student authored paper" from SPSP (Akinola & Mendes, 2008)
2009	Winner of the SAGE Early Career Award from the foundation of Social and Personality Psychology
2011	Awarded the Janet Taylor Spence award for "transformative early career contributions" by the Association for Psychological Science

C. Selected Peer-reviewed Publications (Selected from over 50 peer-reviewed publications)
*indicates graduate student or post-doctoral advisee

Most relevant to the current application

1. Mendes, W. B., Blascovich, J., Hunter, S., Lickel, B., & Jost, J. (2007). Threatened by the unexpected: Challenge and threat during inter-ethnic interactions. Journal of Personality and Social Psychology, 92, 698-716. [Winner of the Gordon Allport Intergroup Relations Prize for best paper of 2007].
2. Mendes, W. B., *Gray, H., Mendoza-Denton, R., Major, B. & Epel, E. (2007) Why egalitarianism might be good for your health: Physiological thriving during inter-racial interactions. Psychological Science, 18, 991-998. PMCID: PMC2430625
3. Mendes, W. B., Major, B., McCoy, S., & Blascovich, J. (2008). How attributional ambiguity shapes physiological and emotional responses to social rejection and acceptance. Journal of Personality and Social Psychology, 94, 278-291. PMCID: PMC2535927
4. *Gray, H., Mendes, W. B., *Denny-Brown, C. (2008). An in-group advantage to detecting intergroup anxiety. Psychological Science, 19, 1233-1237. PMCID: PMC2659396
5. Nock, M. K. & Mendes, W. B. (2008). Physiological arousal, distress tolerance, and social problem solving deficits among adolescent self-injurers. Journal of Consulting and Clinical Psychology, 76, 28-38.
6. Gramzow, R., *Willard, G., & Mendes, W. B. (2008). Big tales and cool heads: GPA exaggeration is related to increased parasympathetic activation. Emotion, 8, 138-144.
7. *Akinola, M. & Mendes, W. B. (2008). The dark side of creativity: biological vulnerability and negative mood leads to greater artistic creativity. Personality and Social Psychology Bulletin, 34, 1677-1686. PMCID: PMC2659536 [Winner of the SPSP prize for best paper for 2008]
8. *Kassam, K., *Koslov, K., & Mendes, W. B. (2009). Decisions under distress: Stress profiles predict anchoring and adjustment estimates. Psychological Science,
9. *Jamieson, J., Mendes, W. B., *Blackstock, E. & Schmader, T. (2010). Turning the knots in your stomach into bows: Reappraising arousal improves performance on the GRE. Journal of Experimental Social Psychology, 46, 208-212.
10. Mendes, W. B. (2010). Links between mind and body across the life span: A case for maturational dualism in the experience of emotion. Emotion Review, 2, 240-244.
11. Koslov, K., Mendes, W. B., **Patjas, P., & Pizzagalli, D. A. (2011). Greater left resting intracortical activity as a buffer to social evaluative threat. Psychological Science, 22, 641-649.
12. *Page-Gould, E., Mendes, W. B., & Major, B. (2010). Intergroup contact facilitates physiological recovery following stressful intergroup interactions. Journal of Experimental Social Psychology, 46, 854-858.

13. *Townsend, S., Major, B.,*Sawyer, P., & Mendes, W. B. (2010). Can the absence of prejudice be more threatening than its presence? It depends on one's worldview. Journal of Personality and Social Psychology, 99, 933-947.
14. Major, B., Mendes, W.B. & Dovidio, J. (in press). The social psychology of intergroup relations: Implications for health disparities. Health Psychology.
15. *Cushman, F., * Gray, K., **Gaffey, A., & Mendes, W. B. (in press). Simulating murder: The aversion to harming others. Emotion.

D. Research Support

Ongoing Research Support

NHLBI 1 RO1 HL079383-01A1 **Major (PI)** 1/1/2006 – 3/31/2012
National Institute of Heart, Lung and Blood
The Effects of Perceived Discrimination on Mental and Physical Health
The major goals of this funded grant are to examine the effects of rejections and discrimination physiological responses associated with physical health.
Role: PI on subcontract

National Institute of Aging R21 AG030632 Kubzansky (PI) 7/1/2009 – 6/30/2012
The biology of resilience: Oxytocin, social relationships and health
This research examines the effects of oxytocin in forming social relationships.
Role: Co-I

National Institute of Aging 1RC2AG036780 1/1/2010 – 12/31/2011
Race-based social stress and health trajectories from adolescence to adult
This funding provides pilot data for the current grant under consideration. The goals are to examine acute reactivity to discrimination among a well characterized group of participants from MADICS. Role: PI on subcontract

Completed Research Support

Robert Wood Johnson Health Disparities Grant (PI) 2007 – 2008
Neuroendocrine and cardiovascular consequences of expecting and experiencing discrimination
The goals of this project are to examine emotional and physiological responses stemming from dyadic social interactions among minority and majority group members when individuals expect and experience discrimination.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Katherine P. Rankin, Ph.D	POSITION TITLE Associate Professor Department of Neurology
eRA COMMONS USER NAME krankin	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Yale University, New Haven, CT	B.A.	1988-1992	Psychology
Fuller Theological Seminary, Pasadena, CA	M.A.	1994-1997	Theology
Fuller Graduate School of Psychology,	Ph.D.	1994-2000	Clinical Psychology
University of California San Francisco, SF, CA	Fellowship	2000-2002	Neuropsychology

A. Personal Statement

My primary research interest is the investigation of neuroanatomic changes that can cause altered social behavior and social behavior in certain neurodegenerative diseases, and I also study the influence of endogenous hormones on cognition in these patients. Dr. Woolley proposes to study the effects of intranasal oxytocin on social cognition and behavior in patients with schizophrenia. My expertise in the assessment of social cognition and behavior in multiple patient populations makes me ideally suited to assist Dr. Woolley in designing and implementing this study. Furthermore, I have extensive experience and proficiency in the statistical analysis of similar complex, multivariate data sets involving multiple cognitive and behavioral measures. I will provide Dr. Woolley with mentorship and hands-on training in these statistical tools.

B. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

1999 – 2000 **Psychology Intern,** Northern CA Health Care System VA – Martinez, CA/UC Davis – Davis, CA
2000 – 2002 **Postdoctoral Fellow in Neuropsychology,** Memory & Aging Center, UCSF – San Francisco, CA
2002 – 2008 **Assistant Professor,** Department of Neurology, University of California San Francisco
2008 – **Associate Professor,** Department of Neurology, University of California San Francisco

Professional Memberships

1994 – 2008 American Psychological Association
1997 – present International Neuropsychological Society
2001 – 2008 Cognitive Neuroscience Society
2003 – present American Academy of Neurology

Honors & Awards

1996 *Clare W. Headington Memorial Scholarship Award* – Fuller School of Psychology
1998 *Faculty and Administration Wives' Memorial Award* – Fuller All-Seminary
2002 *Achievement in Neuropsychology* – UCSF Memory and Aging Center

C. Selected peer-reviewed publications (in chronological order). Do not include publications submitted or in preparation.

1. **Rankin, K.P.,** Kramer, J.H., Mychack, P.M., & Miller, B. L. (2003). Double dissociation of social functioning in frontotemporal dementia. *Neurology, 60*, 266-271. PMCID: PMC2701364
2. Gorno-Tempini, M.L., Dronkers, N.F., **Rankin, K.P.**, Ogar, J.M., Phengrasamy, L., Rosen, H.J., Johnson J.K., Weiner, M.W.,Miller, B.L. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology, 55*(3): 335-346. PMCID: PMC2362399
3. **Rankin, K.P.,** Rosen, H.J., Kramer, J.H., Schauer, G.F., Weiner, M.W., Schuff, N., & Miller, B.L. (2004). Right and left medial orbitofrontal volumes show an opposite relationship to agreeableness in FTD. *Dementia and Geriatric Cognitive Disorders,* 17: 328-332. PMCID: PMC2362501
4. **Rankin, K.P.,** Baldwin, E., Pace-Savitsky, C., Kramer, J.H., & Miller, B.L. (2005). Self-awareness and personality change in dementia. *Journal of Neurology, Neurosurgery, and Psychiatry,* 76: 632-639. PMCID: PMC1739614
5. **Rankin, K.P.,** Gorno-Tempini, M.L., Allison, S.C., Stanley, C.M., Glenn, S., Weiner, M.W., & Miller, B.L. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain, 129*(11)*:* 2945-56. PMCID: PMC2562652
6. **Rankin K.P.**, Liu A.A., Howard S., Slama H., Hou C.E., Shuster K., Miller B.L. (2007). A case-controlled study of altered visual art production in Alzheimer's and FTLD. *Cognitive Behavioral Neurology, 20*(1): 48-61. PMCID: PMC2651227
7. **Rankin, K.P.**, Santos-Modesitt, W., Kramer, J.H., Pavlic, D., Beckman, V., & Miller, B.L. (2008) Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *Journal of Clinical Psychiatry, 69*(1):60-73. PMCID: PMC2735556
8. **Rankin, K.P.**, Salazar, A., Gorno-Tempini, M.L., Pavlic, D., Stanley, C., Glenn, S., Weiner, M.W., & Miller, B.L. (2009). Detecting sarcasm from paralinguistic cues: anatomic and cognitive correlates in neurodegenerative disease. *Neuroimage,* 47(4):2005-15. PMCID: PMC2720152
9. Sollberger, M., Stanley, C.M., Wilson, S.M., Gyurak, A., Beckman, V., Growdon, M., Jang, J., Weiner, M.W., Miller, B.L., & **Rankin, K.P.** (2009). Neural basis of interpersonal traits in neurodegenerative diseases. *Neuropsychologia, 47*(13):2812-27. PMCID: PMC2765796
10. Sollberger, M., Neuhaus, J., Ketelle, R., Stanley, C.M., Beckman, V., Growdon, M., Jang, J., Miller, B.L., & **Rankin, K.P.** (2010). Interpersonal traits change as a function of disease type and severity in degenerative brain diseases. *Journal of Neurology, Neurosurgery, and Psychiatry*. PMCID: PMC3062743
11. Woolley, J.D., Khan, B.K., Murthy, N.K., Miller, B.L., **Rankin, K.P.** (2011) The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *Journal of Clinical Psychiatry.* 72(2): 126-133. PMCID: PMC3076589
12. Sollberger, M., Stanley, C.M., Ketelle, R., Beckman, V., Growdon, M., Kramer, J.K., Miller, B.L., **Rankin, K.P.** (2011). Neuropsychological correlates of dominance, warmth, and extraversion in neurodegenerative disease. *Cortex.* Mar 10 [Epub ahead of print]. NIHMSID: 278447
13. Woolley, J.D., Strobl, E.V., Shelly, W.B., Karydas, A.M., Ketelle, R., Wolkowitz, O.M., Miller, B.L., **Rankin, K.P**. (In press). BDNF serum concentrations show no relationship with diagnostic group or medication status in neurodegenerative disease. *Current Alzheimer Research*. NIHMSID: 299286
14. Lee, S.E., Seeley, W.W.., Poorzand, P., Rademakers, R., Karydas, A., Stanley, C.M., Miller, B.L., **Rankin, K.P.** (In press). Clinical characterization of bvFTD due to FUS neuropathology. *Neurocase.* NIHMSID: 298171
15. **Rankin, K.P.,** Mayo, M.C., Seeley, W.W., Lee, S., Rabinovici, G., Gorno-Tempini, M.L., Boxer, A.L, Weiner, M.W., Trojanowski, J.Q., DeArmond, S.J., Miller, B.L. (In press). Behavioral-variant frontotemporal dementia with corticobasal degeneration pathology: Phenotypic comparison to bvFTD with Pick's disease. *Journal of Molecular Neuroscience.*

D. Research Support.

CURRENT:

Measuring Altered Social Behavior in Neurodegenerative Disease

To adapt existing measures of social cognition for reliable and valid use in neurodegenerative diseases. The resulting battery will 1) operationalize the social criteria for frontotemporal lobar degeneration to improve early diagnosis, 2) identify characteristic patterns of social function in other dementias, 3) provide a valid, normed measure of social function in healthy older adults, 4) link quantitative data about social cognition with structural neuroanatomy.

NIH: 1 R01-AG029577-01 04/1/08 – 03/31/13

Role: **Principal Investigator**

Frontotemporal Dementia: Genes, Images, and Emotions (Project 5: Brain & Behavior)

The goal of the overall program project is to determine the genetic, imaging, and emotional and diagnostic features of fontotemporal lobar degeneration. Project 5 aims to link performance on specific neuroscientifically-based cognitive and behavioral tasks to regional pathology in FTLD measured with neuroimaging.

NIH/NIA: 5 P01AG019724-04 (PI: Miller) 9/1/07 – 8/31/12

Role: **Co-Investigator**

A Hillblom Network Program for the Pre-clinical Identification of Alzheimer's Diseases and Other Age-related Dementias.

The overlying goal of this program is to develop successful strategies for diagnosing and then slowing or preventing the progression from healthy aging or mild cognitive impairment (MCI) to dementia.

The Larry Hillblom Foundation: 2007/2I (Miller) 9/1/07 – 12/31/12

Role: **Consultant**

PAST:

Domain Specific Tasks of Executive Function

The objective of this contract is to develop psychometrically robust Executive Function (EF) measurement tools that are accepted by the neurology clinical trials and clinical research communities.

NIH-NIDS N01-NS 6-2366 (PI: Kramer) 9/31/05 – 8/31/11

Role: **Consultant**

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Vinogradov, Sophia, M.D.	Interim Associate Chief of Staff for Mental Health at the SFVAMC; Professor of Psychiatry, UCSF; Research Scientist, NCIRE
eRA COMMONS USER NAME VINOGRADOV	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University Louis Pasteur, Strasbourg, France	B.S.	1979	Pre-Medical
Wayne State University School of Medicine, Detroit, MI	M.D.	1983	Medicine

A. Personal Statement

The goal of the proposed research is to investigate the effects of intranasal oxytocin on social cognition, neural activity to social stimuli, and social behavior in patients with recent-onset schizophrenia. I will serve as the primary mentor for Dr. Woolley during his CDA. I hold the positions of Interim Associate Chief of Staff for Mental Health at the SFVAMC, and Interim Vice-Chair and Professor of Psychiatry at the University of California, San Francisco. I am Research Co-Director of the Prodrome Assessment, Research, and Treatment program at Langley Porter Psychiatric Institute, UCSF. As PI on three NIMH-funded studies of neuroscience-guided cognitive training in schizophrenia, including one specifically focused on remediation of social deficits, I have the necessary expertise to guide Dr. Woolley in the successful completion of the proposed project. I will supervise him on all aspects of protocol development and implementation, as well as data acquisition, analyses, and interpretation. Previous mentees of mine have developed into successful independent researchers at leading institutions around the country. I am confident that I can provide Dr. Woolley with the appropriate scientific and professional guidance to ensure his success in this project and a strong transition to an independent research career.

Time and Effort Statement: 5% clinical, 45% admininstrative, and 50% research

B. Positions and Honors

Positions and Employment

1983-1987: Intern & Resident in Psychiatry, Stanford University, Palo Alto, CA
1986-1987: Chief Resident in Psychiatry, Palo Alto VAMC/Stanford University, Palo Alto, CA
1987-1989: Research Fellowship in Biological Psychiatry, Palo Alto VAMC, Palo Alto, CA
1989-1992: Medical Director, Adult Outpatient Clinic, CA Pacific Medical Center, San Francisco, CA
1992-1997: Staff Psychiatrist, Psychiatry Outpatient Services, San Francisco VAMC, SF, CA
1992-1998: Assistant Professor of Psychiatry, University of California, San Francisco, CA
1996-present Associate Research Scientist, NCIRE, San Francisco, CA
1997-1999: Chief of Psychiatry Outpatient Services, San Francisco VAMC, San Francisco, CA
1998-2004: Associate Professor of Psychiatry, University of California, San Francisco, CA
1999-present Director of Research and Education, Psychiatric Services, VAMC, San Francisco, CA
2004-present Professor of Psychiatry, University of California, San Francisco

Honors

1995: UCSF Award for Excellence in Teaching.
2002: Academy of Medical Educators, UCSF
2003: Alpha Omega Alpha Society

C. Selected peer-reviewed publications (Selected from 71 peer-reviewed publications)

1. Minzenberg MJ, Fisher-Irving M, Poole JH, **Vinogradov S:** Reduced self-referential source memory performance is related to interpersonal dysfunction in borderline personality disorder. J Pers Disord. 20(1):42-54, 2006.
2. Minzenberg MJ, Poole JH, **Vinogradov S:** Adult social attachment disturbance is related to childhood maltreatment and current symptoms in borderline personality disorder. J Nerv Ment Dis. 194(5):341-8, 2006.
3. **Vinogradov S**, Luks T, Simpson G, Schulman B, Glenn S, Wong A: Brain activation patterns during memory of cognitive agency. NeuroImage. 31(2):896-905, 2006.
4. Minzenberg MJ, Poole JH, **Vinogradov S**: Social-emotion recognition in borderline personality disorder. Comprehensive Psychiatry. 47:468-74, 2006.
5. Minzenberg MJ, Poole JH, **Vinogradov S**: A neurocognitive model of borderline personality disorder: effects of childhood sexual abuse and relationship to adult social attachment disturbance. Development and Psychopathology 20:341-68, 2008.
6. Kumra S, Oberstar JV, Sikich L, Findling RL, McClellan JM, **Vinogradov S**, Charles Schulz S: Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. Schizophr Bull. 34:60-71, 2008.
7. Sanders AR, Duan J, Levinson DF, Shi J, He D, Hou C, Burrell GJ, Rice JP, Nertney, DA, Olincy A, Rozic P, **Vinogradov S**, Buccola NG, Mowry BJ, Freedman R, Amin F, Black DW, Silverman JM, Byerley WF, Crowe RR, Cloninger CR, Martinez M, Gejman PV: No significant association of 14 candidate genes with schizophrenia in a large European ancestry sample: implications for psychiatric genetics. Am J Psychiatry, Epub January 15, 2008.
8. **Vinogradov S**, Luks TLL, Schulman B, Simpson, G. (2008): Deficit in the neural correlate of reality monitoring in schizophrenia patients. Cerebral Cortex 18(11):2532-9.
9. Fisher, M., McKoy, K., Poole, J., **Vinogradov, S**: Self and other in schizophrenia: a cognitive neuroscience perspective. American Journal of Psychiatry 165(11):1465-72, 2008.
10. Brown, S., **Vinogradov, S**., Kremen, W., Poole, J.H., Deicken, R.F., Penner, J.D., McKeague, I.W., Kochetkova, A., Kern, D., Schaefer, C.A (2009). Prenatal infection and executive dysfunction in adult schizophrenia. American Journal of Psychiatry. 166(6): 683-90.
11. Brown, S., Deicken, R., **Vinogradov, S**., Kremen, W.S., Poole, J.H., Penner, J.D., Kochetkova, A., Kern, D., Schaefer, C.A. (2009): Prenatal infection and cavum septum pellucidum in adult schizophrenia. Schizophrenia Research. 108(1-3): 285-7.
12. Gard, D. E., Fisher, M., Garrett, C., Genevsky, A., **Vinogradov, S**. (2009). Motivation and its relationship to neurocognition, social cognition, and functional outcome in schizophrenia. Schiz. Research. 115(1):74-81.
13. Adcock, R.A., Dale, C., Fisher, M., Aldebot, S., Genevsky, A., Simpson, G.V., Nagarajan, S., **Vinogradov, S**. (2009) "When top-down meets bottom-up: Auditory training enhances verbal memory in schizophrenia." Schizophrenia Bulletin. 35(6): 1132-41.
14. Dale, C. L., Findlay, A.M., Adcock, A., Vertinski, M., Fisher, M., Genevsky, A., Aldebot, S., Subramaniam, K., Luks, T.L., Simpson, G.V., Nagarajan, S.S., **Vinogradov, S**. (2010). Timing is everything: Neural response dynamics during syllable processing and its relation to higher-order cognition in schizophrenia and healthy comparison subjects. International Journal of Psychophysiology. 75(2):183-93.
15. Ellman, L. M., Deicken, R. F., **Vinogradov, S**., Kremen, W. S., Poole, J. H., Kern, D. M., et al. (2010). Structural brain alterations in schizophrenia following fetal exposure to the inflammatorycytokine interleukin-8. Schiz Research. 121(1-3): 46-54.
16. Hinkley LB, Owen JP, Fisher M, Findlay AM, **Vinogradov S**, Nagarajan SS (2010). Cognitive impairments in schizophrenia as assessed through activation and connectivity measures of magnetoencephalography (MEG) data. Front. Hum. Neurosci. 3: 73.
17. Kremen WS, **Vinogradov S**, Poole JH, Schaefer CA, Deicken RF, Factor-Litvak P, Brown AS. (2010) Cognitive decline in schizophrenia from childhood to midlife: A 33-year longitudinal birth cohort study. Schizophr Res. 118(1-3):1-5.
18. Schlosser DA, Zinberg JL, Loewy RL, Casey-Cannon S, O'Brien MP, Bearden CE, **Vinogradov S**, Cannon TD. (2010) Predicting the longitudinal effects of the family environment on prodromal symptoms and functioning in patients at-risk for psychosis. Schizophr Res. 118(1-3): 69-75.

19. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, Rumsey JM, Hicks R, Cameron J, Chen D, Chen WG, Cohen LG, deCharms C, Duffy CJ, Eden GF, Fetz EE, Filart R, Freund M, Grant SJ, Haber S, Kalivas PW, Kolb B, Kramer AF, Lynch M, Mayberg HS, McQuillen PS, Nitkin R, Pascual-Leone A, Reuter-Lorenz P, Schiff N, Sharma A, Shekim L, Stryker M, Sullivan EV, & **Vinogradov S**. (2011). Harnessing neuroplasticity for clinical applications. Brain [Epub ahead of print].
20. Aldebot, S., Fisher, M., Garrett, C., Alexander, P., Holland, C., Rose, D., Genevsky, A., Hooker, C., **Vinogradov, S**. (in press). Combining computerized social cognitive training with neuroplasticity-based auditory training in schizophrenia. Clin Schizophr and Relat Psychoses.
21. Hooker, C.I., Tully, L.M., Verosky, S.C., Fisher, M.,Holland, C., **Vinogradov, S**. (in press). Can I trust you? Negative affective priming influences social judgments in schizophrenia. J of Abnormal Psych.

D. Research Support

Ongoing Research Support

R01 MH076989 Mathalon (PI) 05/21/07 - 05/20/12
NIMH
Functional brain abnormalities in the schizophrenia prodrome
Prodromal patients are compared with early illness schizophrenia patients and healthy controls on ERP and fMRI measures of cognitive function. In addition, prodromal patients are followed over 2 years to examine whether ERP and fMRI measures predict conversion to psychosis.
Role: Co-Investigator

R01MH081051 Vinogradov (PI) 04/01/08 – 03/31/13
NIMH
Neuroscience-Guided Cognitive Remediation in Adolescents at Risk for Psychosis
The purpose of this study is to study the efficacy of cognitive remediation on cognition and functional outcome in an adolescent population at high risk for developing schizophrenia.

RO1MH82818 Vinogradov (PI) 08/01/09 – 04/30/14
NIMH
Optimizing Cognitive Remediation Outcomes in Schizophrenia
The purpose of this study is to explicitly and aggressively drive an optimal response to neuroplasticity-based cognitive remediation in schizophrenia in order to maximize treatment response through the addition of a novel computerized remediation application targeting social cognition.

S R01MH081051 Vinogradov (PI) 010/1/09 – 09/30/11
NIMH
Neuroscience-Guided Cognitive Remediation in Adolescents at Risk for Psychosis Supplement
The purpose of this study is to enhance risk prediction through secondary data collection and analysis in an ongoing randomized clinical trial of “neuroplasticity-based” cognitive training for young people at ultrahigh-risk for psychosis.

RO1MH068725 Vinogradov (PI) 02/01/10 – 01/31/15
NIMH
Cognitive Remediation of Schizophrenia in a Community Mental Health Setting
The purpose of this study is to move our investigation of neuroplasticity-based cognitive training in schizophrenia out of the laboratory and in to the community setting to demonstrate its specific utility as a method for restoring cognition and enhancing functional outcome in patients with schizophrenia referred to a community-based supported employment program.

1R21MH086801 (Gard) 07/01/11 – 12/31/13
NIMH

Identification of Specific Motivation Deficits in Schizophrenia. Our overall aims are to 1) provide a clear picture of motivational impairment in schizophrenia, especially as it appears in daily life, 2) investigate specific subcomponents of the construct of *wanting* in Schizophrenia, and 3) begin to examine the relationship between motivational impairment, cognitive impairment, and community outcome.

Completed Research Support

NA Vinogradov (PI) 09/01/06 – 08/30/11
Stanley Foundation
Intensive Remediation for Cognitive Deficits in Patients with First Episode Schizophrenia
The purpose of this study is to apply principles of brain plasticity to a pilot study of an innovative behavioral treatment trial: the neuroscience-guided remediation of specific cognitive deficits in adolescents and young adults with recent-onset schizophrenia.

R24MH081807 Carter (PI) 08/25/08 – 04/30/11
NIMH
Cognitive Control in Schizophrenia
Role: Co-Investigator

R42 MH73358 Merzenich (PI) 10/01/05 – 09/30/08
NIMH
Brain-Plasticity Based Training for Schizophrenia
The major goal of this project is to pilot the electrophysiological response of the brain via MEG to cognitive remediation training in schizophrenia.
Role: Co-Investigator

R01 MH068725 Vinogradov (PI) 03/01/04 – 02/28/09
NIMH
Neuroscience-Guided Cognitive Remediation in Schizophrenia
The major goal of this project is to study the neuropsychological and clinical effect of cognitive remediation in schizophrenia subjects.

S R01 MH68725 Vinogradov (PI) 03/01/06 – 02/28/09
NIMH
Cognitive Remediation in Schizophrenia: Supplement
The major goal of this project is to study the biological and physiological response via fMRI and MEG to cognitive remediation.

S R01 MH68725-02 Vinogradov (PI) 03/01/08 – 02/28/09
NIMH
Cognitive Remediation in Schizophrenia: Supplement
The major goal of this project is to study the effect of cognitive remediation on levels of serum BDNF in schizophrenia subjects and healthy matched controls.

NA Vinogradov (PI) 07/01/05 – 12/30/08
Tauber Foundation
Clinical and Neurocognitive Assessment in Adolescents and Young Adults at High Risk for Schizophrenia
The purpose of this study is to identify the clinical and neurocognitive features that characterize the psychosis prodrome, and those that predict conversion to schizophrenia.

NA Vinogradov (PI) 06/01/09 - -05/31/10
UCSF REAC Grant
Functional Connectivity Analyses of Neural Activity in Schizophrenia Before and After Cognitive Training

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Carter, C. Sue	Professor of Psychiatry Co-Director, The Brain Body Center
eRA COMMONS USER NAME (credential, e.g., agency login) SCARTER	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Drury College, Springfield, MO	BA (summa)	1966	Biology
University of Arkansas, Fayetteville, AR	PhD	1969	Zoology
Michigan State University, East Lansing, MI	NIH postdoc	1969-1970	Zoology (Beh Neuroend)
West Virginia University, Morgantown, WV	NIH postdoc	1970-1971	Zoology (Beh Neuroend)

A. Personal Statement

I am pleased to help mentor Dr. Woolley in his important studies. I have a career-long commitment to understanding the neuroendocrine basis of human behavior. I will help him in the analysis and interpretation of endogenous peptide hormones and in the context of knowledge regarding endogenous neuropeptide systems, including oxytocin (OT) and arginine vasopressin (AVP). OT is of particular interest since this compound is known to have broad effects on social behavior. In addition, we have found that changes in the OT pathway (release of the peptide and changes in receptor methylation in response to OT) may influence individual responses to the detrimental effects of various forms of stressful or anxiety-inducing experiences. My laboratory refined and validated biologically (by taking samples from lactating women and as a function of behavioral experiences), methods for the measurement of OT in bodily fluids, including saliva and blood. We also have applied these methods to measure OT and AVP in samples from clinical populations (e.g. schizophrenia, autism, postpartum depression and Williams Syndrome) and in typical subjects as a function of reproductive state (lactation and the menstrual cycle), social support, wound healing and inflammation. This experience will be used to help Dr. Woolley interpret his own data in the context of biological mechanisms in the behavior of individuals suffering from schizophrenia.

B. Positions and Honors

Positions and Employment Since 1973

1973-1974 Research Fellow, Illinois Dept. of Mental Health, Illinois State Psychiatric Institute, Chicago, IL
1974-1977 Assistant Professor, Departments of Ecology, Ethology and Evolution and Psychology and School of Basic Medical Sciences, University of Illinois, Champaign, IL
1977-1985 Departments Ecology, Ethology and Evolution and Psychology and Program in Neural and Behavioral Biology, University of Illinois, Champaign, IL Associate Professor(1977-1984); Professor (1985)
1981 Visiting Scholar, Department of Physiology, Stanford University Medical School.
1982-1983 Program Associate in Psychobiology, National Science Foundation, Washington, DC
1985-1997 Professor, Department of Zoology, University of Maryland. College Park, MD
1985-2001 Guest researcher, National Institutes of Health, National Institute of Child Health and Human Development (Developmental Endocrinology Branch), Bethesda, MD.
1997-2001 Distinguished University Professor, Department of Biology (formerly Zoology), University of Maryland, College Park, MD
2001-present Professor, Co-Director, The Brain Body Center, Department of Psychiatry, University of Illinois at Chicago. Also appointments in Physiology and Biophysics, and Anatomy and Cell Biology and the College of Nursing.

Other Experience, Professional Membership, and Honors

1970-1971	National Institutes of Health, Postdoctoral Fellowship
1980	Pre-medical Professor of the Year, University of Illinois, Urbana-Champaign, IL
1985	Distinguished Alumni Award, Drury College, Springfield, MO
1993-1998	K05, Research Scientist Award, National Institute of Mental Health
1997-2001	Distinguished University Professorship, University of Maryland, College Park, MD
2001	J. W. Fulbright, College of Arts and Sciences, Distinguished Alumni Award, University of Arkansas, Fayetteville, AR
2004-2005	President, International Behavioral Neuroscience Society
2009	Wayner-NNOXe Pharmaceutical Award for Translational Research, awarded by the International Behavioral Neuroscience Society

C. Selected Peer- reviewed Publications (15) from approximately 250.

Altemus, M., Deuster, P. A., Gallivan, E., **Carter, C. S**., & Gold, P. W. 1995. Suppression of hypothalamic-pituitary-adrenal responses to exercise stress in lactating women. *Journal of Clinical Endocrinology and Metabolism*, 80, 2954-2959.

Carter, C. S., & Altemus, M. 1997. Integrative functions of lactational hormones in social behavior and stress management. *Annals of the New York Academy of Sciences, Integrative Neurobiology of Affiliation*. 807, 164-174.

Carter, C. S. 1998. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology*, 23, 779-818.

Altemus, M, Redwine, L.S., Leong, Y-M., Frye, C.A., Porges, S. W., & **Carter, C. S.** 2001. Responses to laboratory psychosocial stress in postpartum women. *Psychosomatic Medicine* 63, 814-821.

Carter, C.S., Altemus, M., & Chrousos, G.P. 2001. Neuroendocrine and emotional changes in the postpartum period. In *The Maternal Brain*, Edited by C. Ingram and J. Russell, *Progress in Brain Research*, 133, 241-249.

Carter, C.S. Pournajafi-Nazarloo, H., Kramer, K.M., Ziegler, T.W., White-Traut, R, Bello, D., & Schwertz, D. 2007. Oxytocin: Behavioral associations and potential as a salivary biomarker. *Annals of the New York Academy of Sciences,* 1098: 312-322.

Carter, C.S., Grippo, A.J., Pournajafi-Nazarloo, H., Ruscio, M.G., & Porges, S. W. 2008. Oxytocin, vasopressin and sociality. *Progress in Brain Research,* 170: 331-336.

Carter, C.S., Boone, E.M., Pournajafi-Nazarloo, H., & Bales, K.L. 2009. The consequences of early experiences and exposure to oxytocin and vasopressin are sexually-dimorphic. *Developmental Neuroscience,* 31:332-41.

White-Traut, R., Watanabe, K., Pournajafi-Nazarloo, H., Schwertz, D., Bell, A., & **Carter**, C.S. 2009. Detection of salivary oxytocin levels in lactating women, *Developmental Psychobiology*, 51:367-373.

Goldman, M.B., Marlow-O'Connor, M., Torres, I, & **Carter**, C.S. 2008. Diminished plasma oxytocin in schizophrenic patients with neuroendocrine dysfunction and emotional deficits. *Schizophrenia Research*, 98:247-255.

Rubin, L.H., **Carter, C.S**., Drogos, L., Pournajafi-Nazarloo, H., Sweeney, J.A., & Maki, P.M. 2010. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. *Schizophrenia Research* 124:13-21.

Gouin, J.P., **Carter**, C.S., Pournajafi-Nazarloo, H., Glaser, R. Marlarkey, W.B., Loving, T. J., Stowell, J., Kiecolt-Glaser, J.K. Marital behavior, oxytocin, vasopressin and wound healing. *Psychoneuroendocrinology* 35:1082-1090.

Grippo, A.J. Pournajafi-Nazarloo, H., Sanzenbacher, L., Trahanas, D.M., McNeal, N., Clarke, D.A., Porges, S. W., & **Carter**, C.S. (2011). Peripheral oxytocin administration buffers autonomic but not behavioral responses to environmental stressors in isolated prairie voles. *Stress* (in press.)

Goldman, M.B., Gomes, A.M., **Carter**, C.S. & Lee, R. (2011). Divergent effects of two different doses of intranasal oxytocin on facial affect recognition in schizophrenic patients with and without polydipsia. *Psychopharmacology*, 216:101-110.

Rubin, L.H., **Carter**, C.S., Drogos, L., Jamadar, R., Pournajafi-Nazarloo, H., Sweeney, J.A., & Maki, P.M. 2011. Sex-specific associations between peripheral oxytocin and emotion perception in schizophrenia. *Schizophrenia Research* 30:266-270.

D. Research Support
Ongoing and Pending Research Support

RO1. National Institute of Health (NICHD) Carter (PI) 2005-2011
Effects of early experience
Animal model for the effects of early handling on neuropeptides.

RO1 National Institute of Health (NIMH) Carter (PI) 2006-2011,
Neurobiology of Social Support
Animal model: examination of factors contributing to the health benefits of positive social behaviors.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME OF APPLICANT David I. Leitman	POSITION TITLE Research Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) DILEITMAN	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Brooklyn College (CUNY) NY	B.S.	8/97	History/ Psychology
City University (CUNY) NY	Ph.D.	10/06	Cognitive Neuroscience/ Psychology
University of California at Davis	Post-doc	8/07	Cognitive Neuroscience
University of Pennsylvania	Post-doc	8/10	Cognitive Neuroscience

A. Personal Statement

I am a cognitive neuroscientist. My research focuses on social communication, its development and the auditory processing mechanisms for perceiving emotion in music and speech. I apply these interests to the study of neurodevelopmental illnesses and in particular schizophrenia. These interests are a product of a longstanding interest in emotion, music, philosophy and mental illness. Most of my work to date has focused on vocal emotion as conveyed through intonation change (prosody). I have examined vocal affect signal transmission in terms of how such signals are coded, the channels used for such coding, and the receiver's ability to process such signals. This information theoretic approach heavily relies on gestalt principles, perception and the interaction between sensory and higher-order cognitive processes. To conduct my research in emotional and social processing, I employ a variety of the methodologies including structural/functional neuroimaging and electrophysiology. This CDA proposal project and its goal of exploring the putative role of oxytocin on emotional and social communication in schizophrenia, is directly in line with my research interests. Consequently, I am excited to contribute the development and analysis of the data contained in the research proposal of this grant.

B. Positions and Honors

Positions and Employment

1996-1997 Research Assistant, Visual Research Laboratory, Brooklyn College Brooklyn, NY
1998-2000 Research Assistant, Department of Biological Psychiatry, New York State Psychiatric Institute Columbia University, New York, NY
2000-2002 Research Assistant, Department of Medical Genetics, New York State Psychiatric Institute Columbia University, New York, NY
2001-2006 Assistant Research Scientist, Department of Life Sciences, Program in Cognitive Neuroscience in Schizophrenia, Nathan Kline Institute Orangeburg, NY
2006-2007 Post-Doctoral Scholar, Translational Cognitive and Affective Neuroscience Laboratory, UC Davis Imaging Research Center, Sacramento CA
2007-2010 Post-Doctoral Scholar, Brain Behavior Laboratory, University of Pennsylvania, Philadelphia PA

Honors

1995 Accepted into CUNY BA honors program.
1997 Dean's List Brooklyn College Fall, Spring
1997 Graduated Magna Cum Laude, Grade point Average 3.75

2006 CUNY Graduate Center Travel Award for Annual meeting of the Cognitive Neuroscience Society, San Francisco, CA. 2006

2006 Travel award for Analysis of Functional Imaging (AFNI) Training Course at Institute for Clinical Neurophysiology CNR-University of Pisa, Italy

2007 Symposium Chair Travel award, International Congress on Schizophrenia Research Colorado springs CA

2008 Travel Scholarship, Society of Biological Psychiatry annual conference Washington DC

Other Experience

2008 Instructor: Department of Psychology, Undergraduate Program at College of General studies (CGS), University of Pennsylvania. Course: Cognitive Neuroscience.

2008 Mentor: Independent Research Project for the masters program in scientific psychology Drexel University for student Kara Blacker

2008 Co-mentor: Independent Research Project for the Biological Basis of Behavior program UPENN for student Shivika Trivedi

2008 Co-mentor: Independent Research Project for the Biological Basis of Behavior program UPENN for student Jeffery Russ

2009 Co-mentor: Independent Research Project for the Biological Basis of Behavior program UPENN for student Keri Wong

Professional Memberships

Organization for Human Brain Mapping

Society for Neuroscience

Society for Biological Psychiatry

Cognitive Neuroscience Society

International Congress On Schizophrenia Research

C. Selected Peer-reviewed Publications Most Relevant To Application

1. **Leitman DI**, Wolf DH, Laukka P, Ragland JD, Valdez JN, Turetsky BI, Gur RE, Gur RC. Not pitch perfect: Sensory Contributions to Affective Communication Impairment in Schizophrenia. Biol Psychiatry in *2011. PMID: 21762876*
2. **Leitman DI**, Wolf DH, Ragland JD Longhead J, Valdez JN, Javitt DC, Turetsky BI, Gur RC. "It's not what you say, but how you say it": A reciprocal temporo-frontal network for affective prosody. Frontiers of Human Neuroscience. February 26 2010. PMID: 20204074
3. **Leitman DI**, Sehatpour P, Shpaner M, Foxe JJ, Javitt DC. Mismatch Negativity to Tonal Contours Suggests Preattentive Perception of Prosodic Content. Behavior and Brain Imaging. 2009; 3:284-291. PMC Journal – In Process
4. **Leitman DI**, Laukka P, Juslin PN, Saccente E, Butler P, Javitt DC. Getting the Cue: Sensory Contributions to Auditory Emotion Recognition Impairments in Schizophrenia. Schizophr Bull. 2008; [Epub ahead of print]. PMID: 18791077
5. **Leitman DI,** Hoptman M, Foxe JJ, Wylie GR, Nierenberg J, Jalbkowcski M, Lim K, Javitt DC. The Neural Substrates of Impaired Prosodic Detection in Schizophrenia and its Sensorial Antecedents. Am J Psychiatry. 2007; 164:1-9. PMID: 17329473
6. **Leitman DI**, Foxe JJ, Butler PD, Saperstein A, Revheim N, Javitt DC. Sensory contributions to impaired prosodic processing in schizophrenia. Biol Psychiatry. 2005;58:56-61. PMID: 15992523

Additional recent publications of importance to the field (in chronological order)

1. Corcoran C, Gallitano A, **Leitman D**, Malaspina D. The neurobiology of the stress cascade and its potential relevance for schizophrenia. J Psychiatr Pract. 2001;7:3-14. PMID: 15990497

2. Coleman E, Goetz RR, **Leitman D**, Yale S, Stanford A, Gorman JM, Malaspina D. Odor identification impairments in schizophrenia: relationship with demographic measures, clinical variables, and diagnostic subtypes. CNS Spectr. 2002;7:43-8. PMID: 15254448
3. Corcoran C, Mujica-Parodi L, Yale S, **Leitman D**, Malaspina D. Could stress cause psychosis in individuals vulnerable to schizophrenia? CNS Spectr. 2002;7:33-8, 41-2. PMID: 15254447
4. Malaspina D, Dalack G, **Leitman D**, Corcoran C, Amador XF, Yale S, Glassman A, Gorman JM. Low heart rate variability is not caused by typical neuroleptics in schizophrenia patients. CNS Spectr. 2002;7:53-7. PMID: 15254449
5. **Leitman DI**, Ziwich R, Pasternak R, Javitt DC. Theory of Mind (ToM) and counterfactuality deficits in schizophrenia: misperception or misinterpretation? Psychol Med. 2006:1-9. PMID: 16700967
6. Green MF, **Leitman DI**. Social cognition in schizophrenia. Schizophr Bull. 2008;34:670-2. PMID: 18495642
7. **Leitman DI**, Longhead J, Wolf DH, Ruparel K, Kohler CG, Elliott MA, Bilker WB, Gur RE, Gur RC. Abnormal superior temporal connectivity during fear perception in schizophrenia. Schizophr Bull. 2008;34:673-8. PMID: 18550592
8. **Leitman DI**, Wolf DH, Longhead J, Valdez JN, Kohler CG, Brensinger C, Elliott M, Turetsky BI, Gur RE, Gur RC. Ventrolateral Prefrontal Cortex and the Effects of Task Demand Context on Facial Affect Appraisal in Schizophrenia. Social Cognitive and Affective Neuroscience. March 8, 2010. PMID: 20212004
9. **Leitman DI**, Sehatpour P, Foxe JJ, Higgins B, Silipo G, Javitt DC. Sensory deficits and distributed hierarchical dysfunction in schizophrenia. Am J Psychiatry. 2010. PMID: 20478875

D. Research Support:

Ongoing Research Support

K01 MH094689-01 (Leitman,DI) 07/01/11-06/30/16
NIH
Multimodal Neuroimaging of Prosody in Schizophrenia and Developmental Disorders
Role: mentored PI

Completed Research Support

Clinical & Translational Science Award (CTSA), Junior Investigator Pilot Grant (Leitman, DI & Wolf, D)
University of Pennsylvania School of Medicine 8/1/08-731/11
Oxytocin Effects on Social Cognitive Dysfunction in Schizophrenia and Asperger Syndrome
Role: Co-PI

NARSAD Young Investigator Award 7/1/08-6/31/11
National Alliance for Research on Schizophrenia and Depression (NARSAD)
Functional Anatomy of Auditory Emotion Processing in Schizophrenia
Role: mentored PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
PORGES, Stephen W.	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) sporges	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Drew University, Madison, NJ	BA	1966	Psychology
Michigan State University, East Lansing, MI	MA	1968	Psychology
Michigan State University, East Lansing, MI	Ph.D.	1970	Psychology

A. Personal Statement

I have extensive experience developing and applying new technologies in psychophysiology that are applicable to developmental and clinical populations. The theoretical orientation of our laboratory focuses on a phylogenetic model of the autonomic nervous system that I proposed as the Polyvagal Theory (Porges, 1995). The theory provides a reconceptualization of the autonomic nervous system leading to a new understanding of how the autonomic nervous system selectively reacts to specific challenges. The theory incorporates an understanding of the phylogenetic shifts in the neurophysiological mechanisms that mediate autonomic reactivity. The Polyvagal Perspective (see Porges, 2007), challenges researchers to conceptualize autonomic regulation as an important substrate mediating several psychological and behavioral features associated with typical and atypical development. Dr. Woolley's proposed studies are an exciting test of aspects of the Polyvagal Theory. I will provide Dr. Woolley with guidance and mentorship to help Dr. Woolley successfully complete the proposed studies.

B. Positions and Honors

Positions:

8/70 - 8/72 **Assistant Professor of Psychology**, West Virginia University
9/72 - 8/75 **Assistant Professor of Psychology**, University of Illinois at Urbana-Champaign
9/75 - 8/82 **Associate Professor of Psychology**, Program in Neural and Behavioral Biology, University of Illinois at Urbana-Champaign
8/82 - 8/85 **Professor of Psychology**, Institute of Aviation, Medical Information Sciences, Program in Neural and Behavioral Biology, University of Illinois at Urbana-Champaign
8/85 – 6/01 **Professor and Director of Laboratory of Developmental Assessment**, Institute for Child Study, Department of Human Development, University of Maryland
2/98 - 2/01 **Chair**, Department of Human Development, University of Maryland; Director, Institute for Child Study, University of Maryland
2/01 - **Professor and Director**, Brain-Body Center, Department of Psychiatry, University of Illinois at Chicago
7/07 - Professor of BioEngineering, University of Illinois at Chicago

Honors and Awards:

Secretary-Treasurer, Society for Psychophysiological Research (1975-1978)
NIMH K02 Research Scientist Development Award (7/75-12/80; 12/81-7/85)
Board of Directors, Society for Psychophysiological Research (1975-1979, 1986-1989)
Associate Editor, *Psychophysiology* (1983-1987)
Member and Chair of the National Institute for Child Health and Human Development Maternal and Child Health Research Committee (1991-1995)
President, Society for Psychophysiological Research (1993-1994)
President of the Federation of Behavioral, Psychological and Cognitive Sciences, (1999-2002)
American Psychological Association Fellow (Divisions 6 and 7)

Member of the National Academies U.S. National Committee for the International Union of Psychological Science (2006-2009*)*
Association for Psychological Sciences Charter Fellow

C. Selected Peer-reviewed Publications

Most relevant to the current application (5)

Porges SW. (1992). Vagal Tone: A physiological marker of stress vulnerability. *Pediatrics* 90:498-504.
Porges, S.W. (1995). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A Polyvagal Theory. *Psychophysiology*, 32, 301-318.
Porges, S.W. (2003). Social engagement and attachment: A phylogenetic perspective. *Roots of Mental Illness in Children*, Annals of the New York Academy of Sciences, 1008, 31-47.
Porges SW. (2004). Neuroception: A subconscious system for detecting threat and safety. *Zero to Three: Bulletin of the National Center for Clinical Infant Programs* 24:5,9-24.
Porges SW. (2007). The polyvagal perspective. *Biological Psychology* 74:116-143.

Additional recent publications of importance to the field (in chronological order)

Porges SW, Doussard-Roosevelt JA, Portales AL, Greenspan SI. (1996). Infant regulation of the vagal "brake" predicts child behavior problems: A psychobiological model of social behavior. *Developmental Psychobiology* 29:697-712.
Porges SW. (1996). Physiological regulation in high-risk infants: A model for assessment and potential intervention. *Development and Psychopathology* 8:43-58.
Porges SW. (2001). The Polyvagal Theory: Phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology* 42:123-146.
Bazhenova OV, Plonskaia O, Porges SW. (2001). Vagal reactivity and affective adjustment in infants during interaction challenges. *Child Development* 72:1314-1326.
Doussard-Roosevelt JA, Joe CM, Bazhenova OV, Porges SW. (2003). Mother-child interaction in autistic and nonautistic children: Characteristics of maternal approach behaviors and child social responses. *Development and Psychopathology* 15:277-295.
Porges SW. (2003). The Polyvagal Theory: Phylogenetic contributions to social behavior. *Physiology and Behavior* 79:503-513.
Porges SW. (2005). The vagus: A mediator of behavioral and visceral features associated with autism. In ML Bauman and TL Kemper, eds. *The Neurobiology of Autism*. Baltimore: Johns Hopkins University Press, 65-78.
Bazhenova OV, Stroganova TA, Doussard-Roosevelt JA, Posikera LA, Porges SW. (2007) Physiological responses of 5-month-old infants to smiling and blank faces. *International Journal of Psychophysiology* 63:64-76.
Heilman KJ, Bal E, Bazhenova OV, Sorokin Y, Perlman SB, Hanley MC, Porges SW. (2008). Physiological responses to social and physical challenges in children: Quantifying mechanisms supporting social engagement and mobilization behaviors. *Developmental Psychobiology* 50:171-182.
Porges SW. (2008). The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. *Cleveland Clinic Journal of Medicine* 75:S1-5.
Porges SW. (2009). Stress and Parasympathetic Control. In LR Squire, ed. *Encyclopedia of Neuroscience*, Vol. 9, Oxford: Academic Press, 463-469.
Van Hecke AV, Lebow J, Bal E, Lamb D, Harden E, Kramer A, Denver J, Bazhenova O, Porges SW. (2009). Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders. *Child Development*, 80, 1118-1133.
Porges SW, Lewis GF. (2009). The polyvagal hypothesis: Common mechanisms mediating autonomic regulation, vocalizations, and listening. In SM Brudzynski, ed. *Handbook of Mammalian Vocalizations: An Integrative Neuroscience Approach*. Amsterdam: Academic Press, pp 255-264.
Bal E, Harden E, Lamb D, Vaughan-Van Hecke A, Denver JW, Porges SW. (2010) Emotion recognition in children with autism spectrum disorders: Relations to eye gaze and autonomic state. *Journal of Autism and Developmental Disabilities* 40:358-370.

Porges SW, Carter CS. (2010). Neurobiological bases of social behavior across the lifespan. In ME Lamb and AM Freund, eds. Handbook of Life-Span Development: Volume 2, Social and Emotional Development. New York: Wiley, 9-51.

Carter CS, Porges SW. (2010). Social bonding and attachment. In G Koob and E. Adkins-Regan, eds. The Encyclopedia of Behavioral Neuroscience. New York: Elsevier.

Williamson JB, Lewis GF, Grippo AJ, Lamb D, Harden E, Handleman M, Lebow J, Carter CS, Porges SW (2010). Autonomic predictors of recovery following surgery: A comparative study. Autonomic Neuroscience: Basic and Clinical, 156: 60-66.

Grippo AJ, Carter CS, McNeal N, Chandler DL, LaRocca MA, Bates SL, Porges SW (2011). 24-hour autonomic dysfunction and depressive behaviors in an animal model of social isolation: Implications for the study of depression and cardiovascular disease. Psychosomatic Medicine, 73, 59-66.

Dale LP, Keen, J, O'Hara EA, Porges SW. (2010). Infant regulatory disorders: Temperamental, physiological, and behavioral features. The Journal of Developmental and Behavioral Pediatrics. (Epub ahead of print).

Lewis GF, Gatto RG, & Porges SW (2011). Monitoring respiration with infrared thermography. Psychophysiology. (Epub ahead of print).

Porges SW, Carter CS. (in press). Neurobiology and evolution: Mechanisms, mediators, and adaptive consequences of caregiving. In SL Brown, RM Brown, and LA Penner, eds. Self Interest and Beyond: Toward a New Understanding of Human Caregiving. New York: Oxford University Press.

Porges SW, Furman SA. (in press). The early development of the autonomic nervous system provides a neural platform for social behavior: A polyvagal perspective. Infant and Child Development.

Dale LP, O'Hara EA, Schein R, Porges SW. (in press). Nine-month RSA regulation and regulatory disorders predict 54-month behavior problems. Infant Mental Health Journal.

Carter CS, Porges SW. (in press). The neurobiology of social bonding and attachment. In J Decety and J Cacioppo, eds, The Handbook of Social Bonding and Attachment.

D. Research Support

Ongoing

R01 HD053570. Porges (PI). 08/01/2007-05/31/2012. Infant Crying and Developmental Outcome: A Biobehavioral Approach. Project explores the question of whether infants who both cry excessively and have less vagal control of their cardiovascular responses are at greater risk for compromised cognitive and social functioning by the time they are toddlers.

R01MH083782-01 (Maki P, PI). (Porges SW, Co-I). 6/16/09 – 5/31/14. Effects of Estradiol and Phytoestrogens on Stress Responsivity. The project uses a randomized, placebo-controlled trial comparing estradiol and soy supplements to placebo for the treatment of daily anxiety, stress responsivity, objective hot flashes, and cognition in perimenopausal women.

Federal Technical Support Working Group. (Porges SW, PI) 04/02/11-03/31/12. Title: Advanced Remote Automated Physiological analysis by Thermal Imaging. The design, development, testing, and production of a remote automated physiological analysis system via thermal imaging of the human face.

Completed

Charles Start Draper Laboratoy. (Porges SW, PI). 07/01/10 – 06/30/11.
Cambridge, MA Title: R&D in Physiological Research in Human Behavior Models. The proposed research would involve consultation to Draper to shape research objectives and plans in the general area of the physiology of human behavior.

OTHER SUPPORT

WOOLLEY, JOSH

ACTIVE

(Woolley) 9/1/2011 – 9/1/2012 1.2 calendar
UCSF San Francisco Treatment Research Center: $10,000
Pilot Study Program

The Effects of Intranasal Oxytocin on Social Cognition and Social Approach Behaviors in Opioid-dependent Patients receiving Methadone Treatment

This grant will pay for a preclinical trial of using intranasal oxytocin to improve social cognition and promote sociality in opioid-dependent patients on methadone treatment. Role: Principal Investigator.

(Weiss) 1/1/2011 – 1/1/2012 1.2 calendar
UCSF Research Evaluation and Allocation $30,000
Committee Pilot Research Grant

Oxytocin and Unhealthy Interactions in Families of Patients with Recent Onset Schizophrenia: A Novel Biomarker

This grant will pay for a preclinical trial of using intranasal oxytocin to improve interpersonal interactions in families with a child with recent-onset schizophrenia. Role: Co-Investigator.

(Woolley) 7/1/2010 – 7/1/2012 1.2 calendar
UCSF Collaborative Translational Pilot Rsch Grants $20,000
in Child & Adolescent Mental Disorders

The Potential of Oxytocin as a Biomarker and Adjunct Therapy for Adolescents with First-Episode Schizophrenia

This grant will pay for a preclinical trial of using intranasal oxytocin to improve social cognitive deficits in adolescents with recent-onset schizophrenia. Role: Principal Investigator.

OVERLAP

There is no overlap with the proposed study and the aforementioned active grants.

Other Support

MATHALON, DANIEL

ACTIVE

R01 MH076989 Mathalon (PI) 05/21/07 - 05/20/12 2.28 cal
Functional brain abnormalities in the schizophrenia prodrome $313,562 direct
This study proposes to use fMRI and ERP measures of sensory processing, attention, and working memory to assess abnormalities in patients meeting criteria for the prodromal syndrome who are at ultra-high risk for development of schizophrenia. Prodromal patients will be compared with early illness schizophrenia patients and healthy controls on these functional brain measures. In addition, prodromal patients will be followed clinically over two years to examine whether ERP and/or fMRI measures of compromised brain function predict subsequent conversion to schizophrenic psychosis. Role: Principal Investigator

NARSAD Mathalon (PI) 09/15/07 – 09/14/11 (NCE) 0.12 cal
$50,000 direct
Cognitive remediation training in first-episode schizophrenia: Tracking treatment effects with fMRI.
This study proposes to use fMRI to track improvements in brain function in patients with first episode schizophrenia undergoing cognitive remediation training for cognitive dysfunction.
Role: Principal Investigator

S R01 MH081051-01 Vinogradov (PI) 09/01/08 – 02/28/13 0.6 cal
NIMH $50,000 direct
Clinical and Neurocognitive Assessment in Adolescents and Young Adults at Risk for Serious Psychiatric Disorders
The supplement to this study supports the addition of fMRI to examine the effects of cognitive remediation on adolescents at ultra-high risk for psychiatric disorders.
Role: Investigator

R01MH82818-01A2 Vinogradov (PI) 07/01/09 – 06/30/14 0.3 cal
NIMH $444,870 direct
Optimizing Cognitive Remediation Outcomes in Schizophrenia
The purpose of this study is to explicitly and aggressively drive an optimal response to neuroplasticity based cognitive remediation in schizophrenia in order to maximize treatment response.
Role: Investigator

Department of Defense McCaslin (PI) 5/1/2010 – 4/30/2012 0.36 cal
fMRI of PTSD and Chronic Pain Comorbidity $100,000 direct
This study examines functional brain abnormalities in patients with comorbid post-traumatic pain disorder and chronic pain.
Role: Investigator

R01 MH082022 Woods (PI) 09/01/08 – 08/31/14 0.9 cal
8/8 Predictors and Mechanisms of Conversion to Psychosis $424,499 direct
The major goals of this project are to identify predictors and mechanisms of conversion to psychosis in a new sample. Role: Investigator and PI of NCIRE subcontract with Yale University

AstraZeneca Mathalon (PI) 09/01/06 – 06/30/11 (NCE) 0.12 cal WOS
Clinical Translational Neuroscience Studies of Schizophrenia $90,000 direct
This study develops and validates electroencephalographic (EEG) indices of sensory, perceptual, and neurocognitive processes that 1) can be readily measured in both human and non-human primates, 2) are sensitive to the pathophysiology of schizophrenia, and 3) are similarly disrupted in both human and non-human primates by NMDA antagonist, ketamine. Role: Principal Investigator

R01 MH-58262 Ford (PI) 12/01/07 – 11/30/12 1.32 cal WOS
Corollary Discharge Dysfunction in Schizophrenia: ERPs and EEG $244,262 direct
Use EEG and ERPs to study a fundamental neurophysiological deficit in schizophrenia.
Role: Investigator

UCI subcontract Potkin (PI) 03/01/10 – 03/01/12 0.12 cal WOS
$100,500 direct
Contrasting the Brain Effects of Risperdal and Invega with fMRI and PET Scanning
The objective of this protocol is to compare the brain effects of Invega to Risperdal in patients with schizophrenia, focusing on fMRI BOLD signal difference in response to multiple paradigms.
Role: Investigator

N01DA185550 Hinshaw (PI) 04/29/10 – 04/21/12 0.12 cal WOS
NIDA $69,945 direct
Neural Correlates of ADHD (Follow up study to Multimodal Treatment Study of Children with ADHD (MTA) (ARRA Supplement to Base Contract)
The MTA is a six-site, cooperative agreement, now focused on long-term follow-up of 579 young adults with ADHD, Combined type, and 289 local normative comparison subjects. The ARRA Supplement funds (a) intensified sample retention efforts, (b) a mixed-method investigation of young adult subject perceptions of turning points in their lives, and (c) neurocognitive assessment and neuroimaging of a subgroup with particular histories of substance abuse across the longitudinal span of the study.
Role: Investigator and PI of NCIRE subcontract with UC Berkeley.

R21MH087748 Mathews (PI) 06/1/10 – 06/30/12 0.48 cal WOS
Identifying Intermediate Phenotypes for Compulsive Hoarding $157,924 direct
The goal of this project is to conduct a pilot study of work to examine frontally-mediated neurocognitive function in severe compulsive hoarding (SCH) with the ultimate goal of identifying intermediate phenotypes that will be useful for genetic studies.
Role: Investigator and PI of NCIRE subcontract with UCSF.

R01 AT004572-02S1 Eisendrath (PI) 01/01/10 – 02/28/13 1.44 cal
$43,799 direct
Applying Mindfulness-Based Cognitive Therapy to Treatment Resistant Depression
The goal of the proposed research is to use functional MRI (FMRI) to investigate the neural mechanisms by which mindfulness-based cognitive therapy produces clinical improvement in patients with treatment resistant major depressive disorder. Role: Co-Investigator and PI of NCIRE subcontract with UCSF.

DVA 1I01CX000497-01 Ford (PI) 07/01/11– 06/30/15 0.24 cal WOS
$172,703 direct
Neural Connectivity and dysconnectivity in schizophrenia: EEG and fMRI studies
Using resting state activity as the conceptual starting point, simultaneously recorded EEG and fMRI data will be used to study (1) the interaction between resting state activity and task performance, (2) the responsiveness of auditory and visual cortex to probes during resting state activity, and (3) the effect of self-initiated actions on resting state activity, all with the goal of elucidating the pathophysiology of schizophrenia. Role: Co-Investigator

OVERLAP

There is no overlap with the proposed study and the aforementioned active grants.

OTHER SUPPORT

MENDES, WENDY BERRY
ACTIVE

NIHLBI 1 RO1 HL079383-01A1 (Mendes) **National Institute of Heart, Lung and Blood** The Effects of Perceived Discrimination on Mental and Physical Health The major goals of this funded grant are to examine the effects of discrimination on physiological responses	Dates of Approved/Proposed Project Annual Direct Costs 1/1/2006 – 3/31/2012 $2,301,153	Percent Effort 1 month
R21 AG030632 (Kubzansky) **National Institute of Aging** The biology of resilience: Oxytocin, social relationships, and health This research examines the effects of oxytocin in forming social relationships. Role: Co-I	01/01/2009 – 12/31/2012 $948,000	.5 month
1RC2AG036780 (Mendes) **National Institute of Aging** Race-based social stress and health trajectories from adolescence to adult This funding provides pilot data for the current grant under consideration. The goals are to examine acute reactivity to discrimination among a well characterized group of participants from MADICS. Role: PI on subcontract	1/1/2010 – 08/31/2012 $175,675	1 month

OVERLAP

There is no overlap with the proposed study and the aforementioned active grants.

OTHER SUPPORT

Name: **Rankin, Katherine**
Position: Associate Professor in Residence

ACTIVE

1. 1 R01-AG029577-01 (Rankin) 4/15/08 – 3/31/13 7.2 calendar
NIH/NIA $202,950

Measuring Altered Social Behavior in Neurodegenerative Disease

The major goal of this project is to adapt existing measures of social cognition for reliable and valid use in neurodegenerative diseases. The resulting battery will 1) operationalize the social criteria for frontotemporal lobar degeneration to improve early diagnosis, 2) identify characteristic patterns of social function in other dementias, 3) provide a valid, normed measure of social function in healthy older adults, 4) link quantitative data about social cognition with structural neuroanatomy

2. 5 P01AG019724-09 (Miller) 9/01/07 -- 8/31/12 1.2 calendar
NIH/NIA $688,143

Frontotemporal Dementia: Genes, Images, and Emotions (Project 5/DBMC Core)

The goal of the overall program project is to determine the genetic, imaging, and emotional and diagnostic features of fontotemporal lobar degeneration. Dr. Rankin is currently interim director of the Data and Biostatistic Core, and is also funded on Project 5, which aims to link performance on specific neuroscientifically-based cognitive and behavioral tasks to regional pathology in FTLD measured with neuroimaging.

3. N01-NS 6-2366 (Kramer) 9/31/05 – 8/31/11 1.2 calendar
NIH-NINDS $1,590,007 (contract)

Domain Specific Tasks of Executive Function

The objective of this contract is to develop psychometrically robust Executive Function (EF) measurement tools that are accepted by the neurology clinical trials and clinical research communities.

4. 2007/2I (Miller) 9/01/07 – 12/31/12 1.2 calendar
The Larry Hillblom Foundation $450,000

A Hillblom Network Program for the Pre-clinical Identification of Alzheimer's Diseases and Other Age-related Dementias

The goal of this program is to develop successful strategies for diagnosing and then slowing or preventing the progression from healthy aging or mild cognitive impairment (MCI) to dementia.

PENDING

1. 2 P01 AG019724-11 (Miller) 9/01/12 – 8/31/17 3.6 calendar
NIH/NIA *(Priority score: 10 as of 7/26/2011 review)* $1,500,000

Frontotemporal Dementia: Genes, Images, and Emotions

The goal of the overall program project is to determine the genetic, imaging, and emotional and diagnostic features of fontotemporal lobar degeneration. Dr. Rankin has percent effort on the Clinical Core, the Data Management and Biostatistics Core, and Project 4 (Clinical Criteria).

OVERLAP

There is no overlap with the proposed study and the aforementioned active grants.

OTHER SUPPORT

VINOGRADOV, SOPHIA

ACTIVE

R01 MH076989 Mathalon (PI) 05/21/07 - 05/20/12 0.6 calendar months
NIMH $1,962,350
Functional brain abnormalities in the schizophrenia prodrome
The major goals of this project are to show whether ERP and fMRI measures predict conversion to psychosis. Prodromal patients are compared with early illness schizophrenia patients and healthy controls on ERP and fMRI measures of cognitive function. In addition, prodromal patients are followed over 2 years.

R01MH081051 Vinogradov (PI) 04/01/08 – 03/31/13 0.6 calendar months
NIMH $1,677,300
Neuroscience-Guided Cognitive Remediation in Adolescents at Risk for Psychosis
The major goal of this study is to study the efficacy of cognitive remediation on cognition and functional outcome in an adolescent population at high risk for developing schizophrenia.

RO1MH82818 Vinogradov (PI) 08/01/09 – 04/30/14 1.8 calendar months
NIMH $2,192,013
Optimizing Cognitive Remediation Outcomes in Schizophrenia
The major goal of this study is to explicitly and aggressively drive an optimal response to neuroplasticity-based cognitive remediation in schizophrenia in order to maximize treatment response through the addition of a novel computerized remediation application targeting social cognition.

S R01MH081051 Vinogradov (PI) 10/01/09 – 09/30/11 0.3 calendar months
NIMH $130,542
Neuroscience-Guided Cognitive Remediation in Adolescents at Risk for Psychosis Supplement
The major goals of this study is to enhance risk prediction through secondary data collection and analysis in an ongoing randomized clinical trial of “neuroplasticity-based” cognitive training for young people at ultrahigh-risk for psychosis.

RO1MH068725 Vinogradov (PI) 02/01/10 – 01/31/15 2.2 calendar months
NIMH $2,801,737
Cognitive Remediation of Schizophrenia in a Community Mental Health Setting
The major goals of this study is to move our investigation of neuroplasticity-based cognitive training in schizophrenia out of the laboratory and in to the community setting to demonstrate its specific utility as a method for restoring cognition and enhancing functional outcome in patients with schizophrenia referred to a community-based supported employment program.

1R21MH086801 (Gard) 07/01/11 – 12/31/13 1.2 calendar months
NIMH $436,380
Identification of Specific Motivation Deficits in Schizophrenia.
The major goals of this study are to 1) provide a clear picture of motivational impairment in schizophrenia, especially as it appears in daily life, 2) investigate specific subcomponents of the construct of *wanting* in Schizophrenia, and 3) begin to examine the relationship between motivational impairment, cognitive impairment, and community outcome.

PENDING

1R03TW009002 (Vinogradov) 07/01/11 – 12/31/13 1.2 calendar months
NIMH
Computerized Cognitive Training for schizophrenia in Brazil

The goals of this project are: 1) to develop research expertise and a sustainable research infrastructure among psychiatrists in a developing country (Brazil) in the study of cognition in schizophrenia; 2) to modify a neuroscience-based computerized cognitive training program for schizophrenia so that it is adapted for the language and cultural milieu of Brazil; 3) to perform a clinical trial of cognitive training in the context of a developing country.

1P50MH096859 Carter (PI) 06/01/12 – 05/31/17 1.8 calendar months
NIMH
Understanding and Treating Cognitive Dysfunction in Schizophrenia
The goals of this project are to both develop and assess a novel set of cognitive training exercises focusing on the improvement of prefrontal cortical efficiency and integration of processing in posterior cortical sectors

OVERLAP

There is no overlap with the proposed study and the aforementioned active grants.

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2012 *** End Date:** 03/31/2013 **Budget Period** 1

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Joshua		Woolley		PD/PI	168,000.00	9.00			126,000.00	37,800.00	163,800.00
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	Total Funds requested for all Senior Key Persons in the attached file												

Total Senior/Key Person 163,800.00

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Staff Research Assistant GS 5 and Step 1	12.00			37,073.00	11,122.00	48,195.00
1	**Total Number Other Personnel**					**Total Other Personnel**	48,195.00

Total Salary, Wages and Fringe Benefits (A+B) 211,995.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2012 *** End Date:** 03/31/2013 **Budget Period 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.	Tobii x60 Eye Tracker	30,000.00
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	30,000.00

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,000.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees **Total Participant/Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1

Next Period

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2012 *** End Date:** 03/31/2013 **Budget Period 1**

F. Other Direct Costs		Funds Requested ($)
1.	Materials and Supplies	3,345.00
2.	Publication Costs	1,000.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	
6.	Equipment or Facility Rental/User Fees	6,500.00
7.	Alterations and Renovations	
8.	Participant payments	3,960.00
9.	Coursework	1,000.00
10.		
	Total Other Direct Costs	15,805.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	258,800.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				
	Total Indirect Costs			

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	258,800.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1260-Budget Justification.pdf

Add Attachment | Delete Attachment | View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2013 *** End Date:** 03/31/2014 **Budget Period** 2

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Joshua		Woolley		PD/PI	173,040.00	9.00			129,780.00	38,934.00	168,714.00
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	**Total Funds requested for all Senior Key Persons in the attached file**												

Total Senior/Key Person 168,714.00

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Staff Research Assistant GS 5 and Step 1	11.40			33,603.00	10,081.00	43,684.00
1	**Total Number Other Personnel**					**Total Other Personnel**	43,684.00

Total Salary, Wages and Fringe Benefits (A+B) 212,398.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2013 *** End Date:** 03/31/2014 **Budget Period 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	Total funds requested for all equipment listed in the attached file	
	Total Equipment	

Additional Equipment: Add Attachment Delete Attachment View Attachment

D. Travel **Funds Requested ($)**

1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,000.00

E. Participant/Trainee Support Costs **Funds Requested ($)**

1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 2

Next Period

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2013 *** End Date:** 03/31/2014 **Budget Period 2**

F. Other Direct Costs		Funds Requested ($)
1.	Materials and Supplies	3,206.00
2.	Publication Costs	1,000.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	
6.	Equipment or Facility Rental/User Fees	11,050.00
7.	Alterations and Renovations	
8.	Participant payments	4,060.00
9.	Coursework	1,000.00
10.		
	Total Other Direct Costs	20,316.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	233,714.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				
	Total Indirect Costs			

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	233,714.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1260-Budget Justification.pdf

Add Attachment | Delete Attachment | View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2014 *** End Date:** 03/31/2015 **Budget Period** 3

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Joshua		Woolley		PD/PI	178,231.00	9.00			133,673.00	40,102.00	173,775.00
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	**Total Funds requested for all Senior Key Persons in the attached file**												

Total Senior/Key Person 173,775.00

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Staff Research Assistant GS 5 and Step 1	11.40			36,578.00	10,973.00	47,551.00
1	**Total Number Other Personnel**					**Total Other Personnel**	47,551.00

Total Salary, Wages and Fringe Benefits (A+B) 221,326.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2014 *** End Date:** 03/31/2015 **Budget Period 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel **Funds Requested ($)**

1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,000.00

E. Participant/Trainee Support Costs **Funds Requested ($)**

1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees **Total Participant/Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 3

Next Period

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2014 *** End Date:** 03/31/2015 **Budget Period 3**

F. Other Direct Costs		Funds Requested ($)
1.	Materials and Supplies	1,869.00
2.	Publication Costs	1,000.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	
6.	Equipment or Facility Rental/User Fees	11,700.00
7.	Alterations and Renovations	
8.	Participant payments	1,880.00
9.		
10.		
	Total Other Direct Costs	16,449.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	238,775.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				
	Total Indirect Costs			

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	238,775.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1260-Budget Justification.pdf

Add Attachment | Delete Attachment | View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2015 *** End Date:** 03/31/2016 **Budget Period** 4

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Joshua		Woolley		PD/PI	183,578.00	9.00			137,683.00	41,305.00	178,988.00
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	**Total Funds requested for all Senior Key Persons in the attached file**												

Total Senior/Key Person 178,988.00

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Staff Research Assistant GS 5 and Step 1	11.40			38,485.00	11,546.00	50,031.00
1	**Total Number Other Personnel**					**Total Other Personnel**	50,031.00

Total Salary, Wages and Fringe Benefits (A+B) 229,019.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2015 *** End Date:** 03/31/2016 **Budget Period 4**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel		**Funds Requested ($)**
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,000.00

E. Participant/Trainee Support Costs		**Funds Requested ($)**
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees **Total Participant/Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 4

Next Period

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2015 *** End Date:** 03/31/2016 **Budget Period 4**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	899.00
2. Publication Costs	1,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	11,050.00
7. Alterations and Renovations	
8. Participant payments	1,020.00
9.	
10.	
Total Other Direct Costs	13,969.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	243,988.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.			
2.			
3.			
4.			
Total Indirect Costs			

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	243,988.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1260-Budget Justification.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2016 *** End Date:** 03/31/2017 **Budget Period** 5

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Joshua		Woolley		PD/PI	189,085.00	9.00			141,814.00	42,544.00	184,358.00
2.													
3.													
4.													
5.													
6.													
7.													
8.													
9.	**Total Funds requested for all Senior Key Persons in the attached file**												

Total Senior/Key Person 184,358.00

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Staff Research Assistant GS 5 and Step 1	12.00			41,726.00	12,518.00	54,244.00
1	**Total Number Other Personnel**					**Total Other Personnel**	54,244.00

Total Salary, Wages and Fringe Benefits (A+B) 238,602.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2016 *** End Date:** 03/31/2017 **Budget Period 5**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment | Delete Attachment | View Attachment

D. Travel		**Funds Requested ($)**
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,000.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,000.00

E. Participant/Trainee Support Costs		**Funds Requested ($)**
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees **Total Participant/Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 0787638850000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: San Francisco Veterans Affairs

Delete Entry *** Start Date:** 04/01/2016 *** End Date:** 03/31/2017 **Budget Period 5**

F. Other Direct Costs		Funds Requested ($)
1.	Materials and Supplies	946.00
2.	Publication Costs	1,000.00
3.	Consultant Services	
4.	ADP/Computer Services	
5.	Subawards/Consortium/Contractual Costs	
6.	Equipment or Facility Rental/User Fees	7,150.00
7.	Alterations and Renovations	
8.	Participant payments	660.00
9.		
10.		
	Total Other Direct Costs	9,756.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	249,358.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				
	Total Indirect Costs			

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	249,358.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1260-Budget Justification.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

Budget Justification

Personnel:

Joshua Woolley, MD, PhD., PI 9 calendar Months (Research 9 Cal. Months and Clinical 3 cal. Months). 75% of salary plus 30% benefits is requested for all 5 years. Salary requested: $126,000 per year with 3% cost of living increase in years 2, 3, 4 and 5. Dr. Woolley will be primarily responsible for the design and study implementation. He will directly supervise all aspects of the study and will be responsible for hiring and supervising staff, analyzing the data and preparing manuscripts.

Research Assistant: TBD, 12 Calendar Months for years 1 and 5, 11.4 Calendar Months for years 2 and 3, and 4, GS 5, Step 1 with 3% cost of living increase in years 2, 3, 4 and 5. The Research assistant will recruit, schedule and run participants, and organize and analyze data.

Other Direct Costs:

Materials and Supplies:

	Year 1	Year 2	Year 3	Year 4	Year 5
Oxytocin and matched placebo ($44 for 1 bottle of oxytocin and matched placebo)	$2288 (42 subjects for Experiment 1 and 10 subjects for Experiment 2)	$1188 (10 subjects for Experiment 1 and 17 subjects for Experiment 2)	$792 (18 subjects for Experiment 2)	$748 (17 subjects for Experiment 2)	$484 (11 subjects for Experiment 2)

Project dedicated research supplies: $1057 in year 1, $783 in year 2, $855 in year 3, $151 in year 4 and $462 in year 5. This will include purchases of urine toxicology kits, latex gloves, electrodes, electrode gel, subject snacks (this helps with subject compliance with the testing) and testing materials including audiovisual materials.

Total Subject Payments:

	Year 1	Year 2	Year 3	Year 4	Year 5
Subject Payments	$3960 (42 subjects for Experiment 1 at $80 per subject and 10 subjects for Experiment 2 at $60 per subject)	$1820 (10 subjects for Experiment 1 at $80 per subject and 17 subjects for Experiment 2 at $60 per subject)	$1080 (18 subjects for Experiment 2 at $60 per subject)	$1020 (17 subjects for Experiment 2 at $60 per subject)	$660 (11 subjects for Experiment 2 at $60 per subject)

Scanning Time:

	Year 1	Year 2	Year 3	Year 4	Year 5
Scanner Costs	$6500 (10 subjects for Experiment 2 at $650 per subject)	$11050 (17 subjects for Experiment 2 at $650 per subject)	$11700 (18 subjects for Experiment 2 at $650 per subject)	$11050 (17 subjects for Experiment 2 at $650 per subject)	$7150 (11 subjects for Experiment 2 at $650 per subject)

Publication Costs: $1000 per year will be used for the cost of publication.

Travel Expenses: $1000 per year will be used to pay for travel to and registration at scientific conferences for the principal investigator.

Course Work: $1000 per year for the years 1 and 2 will be used to pay for course registration. Courses will include:

1. **Medical Imaging Informatics. 170.03 Department of Biological & Medical Informatics, UCSF**.
2. **Short course on Statistical Parametric Mapping for Functional Neuroimaging. Wellcome Trust Centre for Neuroimaging, University College London.**
3. **Introduction to Linear Models, 192, Course Director: Division of Biostatistics, UCSF.**
4. **Biostatistical Methods for Clinical Research III. 209 Division of Biostatistics, UCSF.**
5. **Analysis of Neural and Behavioral Data. 248 Department of Neuroscience, UCSF.**

Startup costs: $30,000 for year 1. We will purchase the X60 eye-tracker system from Tobii Technology Inc. This is a standalone device that allows subjects' eye-gaze to be unobtrusively tracked in multiple set-ups including while subjects view a projection screen, a monitor, physical objects, and real world scenarios. This device will allow me to track subjects' eye-gaze during computerized tasks in Experiment 1 (Aim 1 and 2).

RESEARCH & RELATED BUDGET - Cumulative Budget

		Totals ($)
Section A, Senior/Key Person		869,635.00
Section B, Other Personnel		243,705.00
Total Number Other Personnel	5	
Total Salary, Wages and Fringe Benefits (A+B)		1,113,340.00
Section C, Equipment		30,000.00
Section D, Travel		5,000.00
1. Domestic	5,000.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		76,295.00
1. Materials and Supplies	10,265.00	
2. Publication Costs	5,000.00	
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees	47,450.00	
7. Alterations and Renovations		
8. Other 1	11,580.00	
9. Other 2	2,000.00	
10. Other 3		
Section G, Direct Costs (A thru F)		1,224,635.00
Section H, Indirect Costs		
Section I, Total Direct and Indirect Costs (G + H)		1,224,635.00
Section J, Fee		